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Award Number:
W81XWH-07-1-0234

TITLE:
Ethnicity and Prostate Cancer: Vitamin D Genetic and Sociodemographic Factors

PRINCIPAL INVESTIGATOR:
Kathleen C. Torkko, PhD

CONTRACTING ORGANIZATION:
University of Colorado Health Sciences Center
Aurora, CO 80045-0508

REPORT DATE:
March 2009

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Annual Summary

PREPARED FOR:
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6. AUTHOR(S)
Kathleen C. Torkko, PhD, MSPH, MS

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
During the 2nd year of the grant, genotyping and sociodemographic survey development and distribution was started and is on-going. The sociodemographic survey was developed, tested, and approved by the local internal review board. Initial distribution of the survey was carried out in January 2009. A second mailing is currently underway. So far approximately 50% of men have responded. Men who have not responded to two mailings will be asked to complete the survey during their annual study visits to the clinic. Difficulties with the genotyping technology resulted in a delay in completing the planned genetic analysis. Problems are currently being solved and the genotyping should be completed by summer 2009 with additional potentially relevant polymorphisms being added. The grantee has taken two classes related to her work (Database Management Using SAS and Statistical Analysis for Microarray Technology) and taught a graduate level epidemiology class with a focus on health disparities in Spring 2008. She attended the Science of Health Disparities conference in Carefree, AZ, from February 3-6, 2009. She was also spoke about health disparities in prostate cancer screening at a company-sponsored event in Dallas, TX on February 21, 2009.

15. SUBJECT TERMS
Prostate cancer, health disparities, training, vitamin D receptor, genetics, sociodemographic factors, race/ethnicity

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Annual Report (Year 2 of 3): March 2009

Contract #: W81XWH-07-1-0234
Grant#: PC060447
PI: Kathleen C. Torkko, PhD, MSPH
Title: Ethnicity and Prostate Cancer: Vitamin D Genetic and Sociodemographic Factors

Introduction

The main purposes of this grant are to provide opportunities for the principle investigator to expand her PhD work and to receive training in cancer health disparity research, specifically in prostate cancer. This training program involves meeting with mentors for guidance, taking classes pertinent to her research and training objectives, and attending appropriate conferences.

Her research work is on differences in vitamin D receptor (*VDR*) genetic relationships to prostate cancer between non-Hispanic White (NHW) and Hispanic White (HW; mainly of Mexican origin) men in the SABOR (San Antonio Biomarkers Of Risk for prostate cancer) study run by researchers at the University of Texas Health Sciences Center, San Antonio (UTHSCSA). Hispanic men have been a focus of Dr. Torkko's PhD research for two reasons: they comprise the largest minority population in the SABOR study, and they are a largely understudied population in prostate cancer and genetic epidemiology. Understanding the relationship of genetics to prostate cancer and how this relationship varies by race/ethnicity can help elucidate racial differences seen in prostate cancer diagnosis, treatment, and survival.

This grant allows Dr. Torkko to increase the number of genes and genetic polymorphisms studied to examine the effects on risk for prostate cancer by ethnicity of gene-gene interactions between the vitamin D receptor (*VDR*) gene and other genes in the metabolic pathway of vitamin D and testosterone.

Another objective of this proposal is to determine if sociodemographic factors differ between NHW, HW, and potentially African American men (if numbers increase) in the SABOR study and if a relationship exists between sociodemographic and genetic factors. This will be accomplished by developing and conducting a sociodemographic survey in the SABOR population.

The support provided by this Traineeship award is providing Dr. Torkko opportunities to develop as an independent prostate cancer epidemiology researcher and to further develop her areas of expertise by providing opportunities to explore differences in prostate cancer by race/ethnicity.

Body

Prostate Cancer Training Program Progress

Mentorship/Collaborations

Dr. Torkko has met with the members of her mentorship panel who have provided guidance on the development of current projects. Dr. Scott Lucia, the primary mentor, an expert prostate cancer pathologist, employs Dr. Torkko as an epidemiologist/statistician in the Prostate Cancer Research Laboratory (PCRL) in the Department of Pathology at the University of Colorado Denver (UCD). Dr. Lucia has further developed Dr. Torkko's involvement in the prostate cancer biorepository at UCD. Dr. Torkko assists managing the patient database and developing research using available resources. This will lead to other funding opportunities. Dr. Lucia is also providing opportunities for first authorship on a paper involving research projects in the PCRL. Specifically, Drs. Lucia and Torkko (as PI) recently wrote an R01 grant through an NIH/NIDDK funding mechanism to complete the data analysis of a project studying the association of the inflammatory process and the progression of benign prostatic hyperplasia (BPH). Dr. Torkko will be the primary author on any publications resulting from this collaboration. Meetings with Dr. Robin Leach and Dr. Ian Thompson during a visit to San Antonio, TX, in July, 2008, resulted in more collaborative work on the associations of genetic variation (*e.g.*, TMPRSS-ERG gene fusions) with prostate cancer, specifically in Hispanic men. Preliminary data collection is underway to prepare for grant submissions. Dr. Torkko is currently collaborating with her Texas colleagues on a

challenge grant application about genetic variation in the 5-alpha reductase gene (*SRD5A2*) and its association with BPH.

Further collaborations have been made with researchers at the University of Washington, Seattle, WA. Dr. Torkko will be a PI on a subcontract for a grant written by Dr. Ulrike Peters that will propose to study vitamin D pathway genetic variation and correlations with diet and serum measures of vitamin D status in the Prostate Cancer Prevention Trial cohort. Dr. Torkko will be responsible for the analysis of gene-gene interactions between vitamin D and androgen pathway genes.

Dr. Torkko has taken a new direction in her health disparity research. She is collaborating with researchers and physicians in the Department of Surgery, Section of Urology, to understand health disparities in screening for prostate cancer. She is the PI on a grant submitted to the State of Colorado to increase education about and access to prostate cancer screening in rural Colorado. An important group for this outreach is Hispanic men. Decisions about funding should be completed by April 2009.

Scientific Conferences

As part of the training for the grant, Dr. Torkko is expected to attend scientific conferences chosen to be relevant to prostate cancer, genetic epidemiology, and/or health disparity/cultural competency. Funds have been allocated to attend at least one conference each funded year. In the 2008-09 grant period, Dr. Torkko attended the second American Association of Cancer Researchers conference on "The Science of Cancer Health Disparities in Racial/Ethnic Minorities and Medically Underserved" in Carefree, AZ, from February 3-6, 2009. As research data become available and analyses mature, it is expected that abstracts will be submitted for future conferences.

Based on her work with health disparities and interests in screening issues, Dr. Torkko was invited to give a lecture at an industry-sponsored meeting on the PCA3 urine test for the detection of prostate cancer. She spoke on race and screening for prostate cancer (see PowerPoint slides of the presentation in Appendix A)

Coursework

As part of the training for the grant, Dr. Torkko is expected to continue her education by taking relevant classes. Dr. Torkko took two classes within the timeframe of the second year of the grant. In the Fall semester 2008, she took two classes (syllabi in Appendix B) offered by the Department of Biostatistics and Informatics in the School of Public Health, University of Colorado.. Due to the large datasets that Dr. Torkko must manage for her data collection and analysis, she took the SAS Database Design and Management class (BIOS 6680). This course allowed Dr. Torkko to improve her SAS skills and to learn more about database design and structured query language (SQL) that allows communication between different database programs. She also took a class that taught the use of R, a free statistical program that researchers at the University of Texas Health Sciences Center San Antonio use for their genetic analyses. This class taught the use of R to analyze large, publically available datasets, specifically for gene expression datasets. She received an "A" in both classes (see transcript in Appendix C).

In the Spring semester 2008, Dr. Torkko taught the Introductory Epidemiology class (HBSC 4001/5001) for the Health and Behavior Sciences Department at the UCD. She made health disparities a focus of the class (see course syllabus in Appendix D). She had her students write a final project on a cancer of their choice about the epidemiology of the cancer and to identify an area where a health disparity exists. Dr. Torkko developed a 90-minute lecture on health disparities (see Appendix E for PowerPoint slides). Teaching this class has given Dr. Torkko invaluable experience and should lead to other teaching and career development opportunities.

Research Project Progress

Sociodemographic Survey

Specific Aim #1: Collect sociodemographic information on SABOR participants using a questionnaire and determine whether sociodemographic factors relating to prostate cancer

screening, diagnosis, and treatment differ by race/ethnicity in the SABOR study. Differences in proportions or frequencies of sociodemographic factors will be tested by racial/ethnic group in men with prostate cancer.

Development and IRB-approval has been obtained and the first mailing of the survey to study participants has been completed. The second mailing to non-responders is currently underway. Approximately 50% of SABOR participants have responded. Men who do not return the survey after the second contact will be asked to complete a form during their annual study visit. Data entry will commence in May 2009. Double entry of all forms will be done and discrepancies will resolved to ensure data entry integrity. Data analysis will be completed by the end of summer. A copy of the survey is included in the Appendix F.

Single Nucleotide Polymorphisms

Specific Aim #2: Determine whether VDR polymorphisms, haplotypes, and gene-gene interactions differ by race/ethnicity. Men will be genotyped for VDR, CYP27B1, and CYP24 polymorphisms. A genetic association case-control study will be performed looking for associations of these polymorphisms and haplotypes with prostate cancer.

The first step of the research plan was to identify a panel of ingle nucleotide polymorphisms (SNPs) for the genes of interest. With the assistance of Dr. Robin Leach at UTHSCSA, a panel of 21 *VDR* SNPs, and 31 SNPs in vitamin D associated genes (*CYP27B1, CYP24A1, PDF*) has been assembled (see Appendix G for a list of the SNPs). These SNPs were chosen as tag SNPs to identify known haplotypes in each gene. As part of her research, Dr. Leach is studying genes in the testosterone pathway and has developed an extensive panel of tagSNPs. There will be opportunities for Dr. Torkko to use these SNPs to study gene-gene interactions between vitamin D and testosterone metabolic pathway genes.

Difficulties with the new technology to genotype the panel of SNPs led to delays in genotyping. Some important SNPs failed quality control and need to be redone. A new panel is being developed using a slightly different technology for those SNPs. Additional SNPs that have appeared in the literature since the original list was chosen will be added (see Appendix G). Genotyping should be completed by the end of the summer when analysis with the completed survey can be started (see specific Aim #3).

Specific Aim #3: Determine the combined relationships of sociodemographic, clinical, /pathological, and genetic factors to prostate cancer and if these relationships differ by race/ethnicity.

This aim will need to wait for completion of the previous two aims. Analysis should commence in the Fall and be completed by the end of the year.

Key Research Accomplishments

In the second year of the grant, the key accomplishments were the publication of one paper in *Clinical Cancer Research* (Torkko *et al, Clin Cancer Res* 2008;14:3223-9; see Appendix H for first page of published paper) based on the results from Dr. Torkko's PhD work. The grant was acknowledged in the paper as it allowed time and resources to complete the work and get it published. The main finding of the Torkko paper was that the vitamin D and testosterone pathways interact to increase risk for prostate cancer in NHW and HW men, and this interaction appears to differ slightly by ethnicity. The *SRD5A2* V89L VV genotype interacts with *VDR Fok*I TT/CT genotypes in NHW men and *VDR* CDX2 GG genotypes in HW men to increase risk for prostate cancer.

In recognition of her work and contributions to the Department and to the University, Dr. Torkko was promoted to Assistant Professor in July 2008.

Reportable Outcomes

Other than the paper listed in the section above for the research part of the grant, reportable outcomes that are related to the training activities of the grant and are in the Appendix as indicated above. These include the syllabus for the Introductory Epidemiology class, the transcript for the classes taken during the second year, and copies of PowerPoint presentations of lectures.

Conclusions

A substantial amount of work has been done for the first two years of the grant, but much work still remains, particularly for the research plan. The training part of the grant has been successful in increasing knowledge and understanding of prostate cancer epidemiology and issues of health disparities in cancer and has led to opportunities for collaboration Additional classes are planned for the fall and spring semesters in the next academic year. The research portion of the grants needs to take priority for the third year to complete the genotyping and to conduct all analyses and preparation of manuscripts.

References

Torkko KC, van Bokhoven A, Mai P, Beuten J, Balic I, Byers TE, Hokanson JE, Norris JM, Baron A, Lucia MS, Thompson IM, and Leach RJ. VDR and SRD5A2 Polymorphisms Combine to Increase Risk for Prostate Cancer in Non-Hispanic White and Hispanic White Men. *Clin Cancer Res* 2008 (May); 14:3223-9

APPENDICES

APPENDIX A: February 21, 2009 Guest Lecture in Dallas, TX

(On next page)

Racial Issues in Prostate Carcinoma Detection, Including Data on PCA3 from PCAW

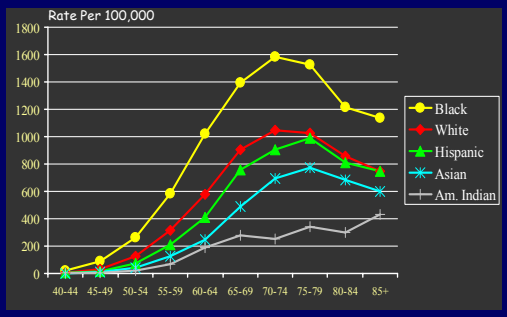
Kathleen C. Torkko, PhD, MSPH, MS

Avero Diagnostics Meeting

Dallas, TX

February 21, 2009

Risk Factors for Prostate Cancer: Increasing Age and African American Race



SEER Crude Rates for Prostate Cancer Incidence by Race and Age, 1992-2001

Source: seer.cancer.gov/faststats

Prostate Cancer: Mostly Commonly Diagnosed and Second Leading Cause of Cancer Death in US Men

Total Cancer Cases in 2008: 745,180

Prostate	25%
Lung & bronchus	15%
Colon & rectum	10%
Urinary bladder	7%
Melanoma of skin	5%

Total Cancer Deaths: 294,120

31%	Lung & bronchus
10%	Prostate
8%	Colon & rectum
6%	Pancreas
4%	Leukemia

2008 Estimated US Cancer Cases and Deaths in Men

Source: American Cancer Society, 2008.

Prostate cancer kills enough American men in 2.5 years to fill Invesco Field at Mile High

What is screening?

Application of a test to detect a potential disease or condition in people with no known signs or symptoms of that disease or condition

Common screening tests. David M. Eddy, editor. Philadelphia, PA: American College of Physicians, 1991

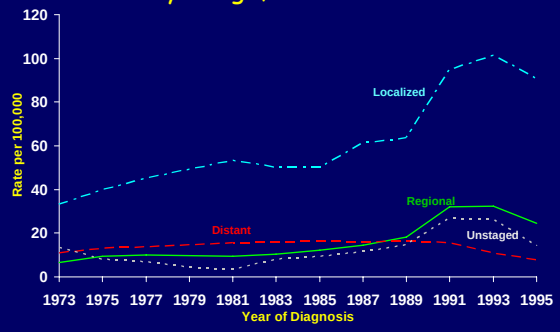
What Makes a Good Screening Test?

- Accurate and reliable
- Relatively simple and inexpensive
- Safe
- Workup of false positives is safe
- Convenient and acceptable to providers and patients

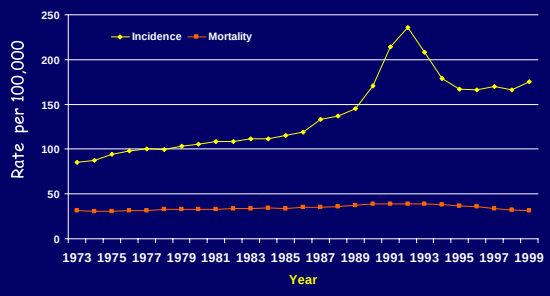
Goal is to reduce morbidity and/or mortality

- Not just early case detection

Prostate Cancer Incidence Rates by Stage, 1973-1995



Prostate Cancer Trends in Incidence and Mortality, 1973-1999



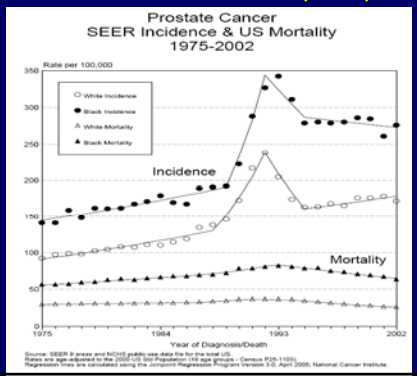
Key Issues of Screening and Early Treatment

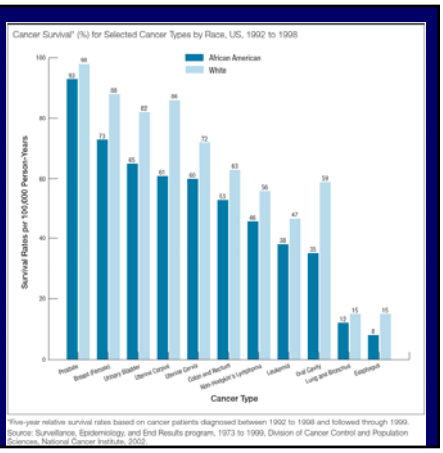
Does screening extend men's lives?
- Decrease in mortality/morbidity

Does screening lead to problems for men?
- False-positives
- Overdiagnosis
- Side effects of treatment

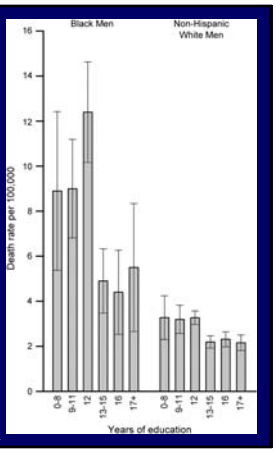
Do the benefits outweigh the harms?

Prostate Cancer Trends by Race, 1975-2002: Evidence of Health Disparity





Prostate cancer mortality rates, by education level and race, for men aged 25-64 years in the United States, 2001



Albano J D. *J Natl Cancer Inst* 2007 99:1384-1394

Health Care Disparities in Access

A study of the U.S. national cancer registry (SEER) found that:

African-American and Hispanic men had longer time intervals between diagnosis and receipt of medical monitoring visit.

Nearly 6% of African-American men and 5% of Hispanic men as compared to 1% of white men did not have any medical monitoring visits or procedures during the 60-month follow up period.

Source: Shavers VL, Brown ML, Klabunde CN, Potosky AL, Davis WW, Moul JW, Fahey A. "Race/ethnicity and the intensity of medical monitoring under 'watchful waiting' for prostate cancer. Medical Care, March 2004, 42 (3):239-250

Why is there a Prostate Cancer Health Disparity in African American Men?

Reasons for disparities unclear

- Diet?
- Access to health care?
- Trust in health care system?
- Genetic susceptibility?

Racial Disparity: Sociology or Biology?

Sociology

Low income associated with advanced stage at diagnosis

African American men are more likely to not receive aggressive treatment

Biology, African American men have:

Higher PSA levels prior to treatment

Evidence of more high grade PIN on biopsy

Larger tumors and higher Gleason scores at same PSA values

Higher rates of biochemical failure after surgery

Reasons African American Men Do Not Get Screened for Prostate Cancer:

- Lack of insurance
- Lack of transportation
- Distrust of medical test for prostate cancer
- Don't think they will get prostate cancer
- Associate cancer with death.
- Fear is the major reason why they do not participate in prostate cancer screening.

What Can be Done to Decrease Health Disparities in African American Men?

Improve screening rates for earlier detection

Evidence that in low-income, uninsured men underdetection and undertreatment are significant concerns

Need for education in community

Implement appropriate treatment depending on prognostic factors

Need to increase awareness of treatment options

Prostate Cancer Awareness Week

Former U.S. Secretary of State Colin Powell, a prostate cancer survivor, urges men to be screened regularly for prostate cancer.

Prostate Cancer Awareness Week
September 14 – 20, 2008

"It's Time."
Get Checked

Log on to www.pcaw.com to find a screening site near you.

PCEC PROSTATE CANCER EDUCATION COUNCIL

get checked

APPENDIX B : Syllabi for Courses Taken

Biostatistics 6660 (BIOS-6660/BIOI-7660)
Statistical Analysis for Microarray Technology
Fall 2008

Instructor: Tzu Lip Phang **Lecture:** MW 12:00-12:50pm
Phone: (303) 315-0893 **Classroom:** Ed 2 South L28-2201
E-mail: tzu.phang@ucdenver.edu **Office:** TBA
Office Hours: MW 1-2pm (or by appointment)

Prerequisites: BIOS 6611 or graduate level statistics course with consent of instructor

Course Description: This course provides students with hands on experience in analyzing full-scale microarray data using the statistical software R, and its packages from the Bioconductor consortium.

Course Objectives: After completion of the course, students will be able perform a complete microarray data analysis project from start to finish, including exploring the nature of the dataset, selecting significant genes for the hypothesis being tested, interpreting the biological meaning of the results, and learning to work with existing public datasets. All these will be accomplished using the free open-source statistical software R.

Evaluation:

Homework	60%
Participation	10%
Final Project	30%

Suggested Texts:
Data Manipulation with R
Authors: Phil Spector
Publisher/Year: Springer, 2008 *ISBN*: 0387747303
The R book
Authors: Michael J. Crawler
Publisher/Year: Wiley, 2007 *ISBN*: 0470510242

Required Work:
- Homework assignments: There will be 5 problem sets for the semester.
- Participation: This is a hands-on statistics software course, all students will be expected to help each others in fixing bugs, as well as to solve problems using outside web resources.
- Final Project: Students will create a final project that utilize dataset from public repositories and apply what they learned from the course.

Assignments and Final Project: Late homework is not accepted without prior permission from the instructor. Students are encouraged to work together on homework assignments, however, the assignment handed in must represent the student's own work. Students are not to work together or discuss the final project**.**

Software: Students will use the free open-source R statistical computation tool for all works in this course

Academic Integrity: You are responsible for being attentive to or observant of campus policies about academic honesty as stated in the University's Student Conduct Code (see http://thunder1.cudenver.edu/studentlife/studentlife/discipline.html). Plagiarism is the use of another person's words or ideas without crediting that person. Plagiarism and cheating will not be tolerated and may lead to failure on an assignment, in the class, and dismissal from the University (see College of Liberal Arts and Sciences guidelines http://thunder1.cudenver.edu/clas/AcademicIntegrity.htm)

Student Code: Adherence to the Student Conduct Code is expected (see http://thunder1.cudenver.edu/studentlife/studentlife/discipline.html). Please turn off beepers and cell phones during class.

Students with Disabilities: The University of Colorado at Denver and Health Sciences Center is committed to providing reasonable accommodation and access to programs and services to persons with disabilities. Please contact me if you need special academic accommodations.

Course Schedule *(Subject to Revision)*

Date	Home Work	Room	Lecture/ Laboratory	Topic
Aug 25			Lecture 1	Class Overview / R installation
27		CTL1501	Laboratory 1	Introduction to R and Bioconductor
Sept 1				NO CLASS – Labor Day Holiday
3		CTL2201	Lec 2 / Lab 2	R primer 1
8		ORI	Lec 2 / Lab 2	R primer 2
10	No 1 out	CTL2201	Lec 2 / Lab 2	R primer 3
15		CTL2201	Lecture 3	Data processing – one color system
17		CTL2201	Laboratory 3	bioC affy package
22	No 1 due	CTL2201	Lecture 4	Quality control
24		CTL2201	Laboratory 4	bioC affyQCReport package
29		CTL2201	Lecture 5	Differential expression & multiple testing
Oct 1	No 2 out	CTL2201	Laboratory 5	Genefilter, genefinder and multitest
6		CTL2201	Lecture 6	2 colors system, part 1
8		CTL2201	Laboratory 6	Data Processing – 2 colors system
13	No 2 due	ORI	Lecture 7	2 colors system, part 2
15	No 3 out	CTL2201	Laboratory 7	Quality control and differential expression
20		CTL2201	Lecture 8	MIAME and public repository
22		CTL2201	Laboratory 8	GEOquery and GEOmetadb
27	No 3 due	CTL2201	Lecture 9	Gene annotation
29	No 4 out	CTL2201	Laboratory 9	Annaffy and biomaRt
Nov 3		CTL2201	Lecture 10	Unsupervised clustering
5		CTL2201	Laboratory 10	Hierarchical, K-means, SOM, etc
10	No 4 due	ORI	Lecture 11	Supervised clustering
12	No 5 out	CTL2201	Laboratory 11	TBA
17		CTL2201	Lecture 12	Gene set enrichment analysis
19		CTL2201	Laboratory 12	GSEA broad institute
24	No 5 due	CTL2201	Lecture 13	Handling huge dataset
26		CTL2201	Laboratory 13	Xps package
Dec 1		CTL2201	Lecture 14	Final project discussion
3		CTL2201	Laboratory 14	Final project help
8		ORI	Laboratory 14	Final project help … continue …
10		CTL2201		Final project due

Syllabus for BIOS6680:
SAS Database Design and Management
Fall 2008

Instructor:
Jessica Bondy, M.H.A
Office: MS 1602-B
Phone: 315-8021
E-mail: Jessica.Bondy@ucdenver.edu
Lecture: 10 – 11:30 Tues, Thurs.L-28-2305 except as noted on schedule
Labs (optional): 12:30-1:30 Tues.
P18-CTL-1309
Web site: https://blackboard.cudenver.edu

I. Goal:

The goal of this course is to introduce students to SAS programming, specifically how SAS can be used to manipulate data and prepare it for analysis: inputting, recoding, reformatting, subsetting, and merging data, as well as writing simple reports. The last third of the class introduces the ideas behind database design, such as normalization, referential integrity, role-based security, transactions, views, and forms design. This course addresses two competencies: 20) evaluate integrity and comparability of data and 22) apply data collection processes, information technology applications and computer system storage strategies to research projects.

II. Objectives:

Students will be able to:

- execute SAS interactively through the Windows graphical user interface
- import data from RDBMS', spreadsheets, and ASCII files into SAS datasets using the Input/Infile statements or ODBC connections
- use SAS Libraries to store permanent SAS datasets and user formats.
- differentiate between the DATA and PROC steps.
- use the Set, Merge and Update statements to manipulate SAS datasets for subsequent, modifications, analyses and reports.
- manipulate information using procedural programming structures provided within the SAS Data Step (e.g. Do, Do Until, Do While, If/Then/Else and Arrays).
- validate and/or re-code data using a variety of methods
- incorporate SAS functions into programs to assist in manipulating information for analysis purposes.
- use the Put/File statements to create ASCII data files and reports.
- read and write SAS macros
- use procedures like CONTENTS, PRINT, and SORT to operate on existing SAS datasets.
- interleave SAS procedures and data steps to accomplish analysis and management of research data.
- create random samples

III. Evaluation:

Homework will be assigned each Thursday and must be handed in at the beginning of class on the following Thursday. Because I may discuss the solution to homework problems in class, no late homework will be accepted. If you must miss a class, please turn in your homework early or let me know as soon as possible so that I can assign an alternate homework problem to you.

Homework may be worked on collaboratively unless I tell you otherwise. There will be at least two assigmments that must be completed on your own.

IV. Texts:

Required:

Delwiche, Lora D. and Slaughter, Susan J. The Little SAS Book, A Primer, 3rd edition, SAS Publishing, 2003.

V. Schedule:

Week	Date	Topics	Readings
1.1	8/26	Class expectations and logistics, examples of problems with data management	
1.2	8/28	The Windows Environment, SAS Display Manager, PROC and DATA steps	1.1-1.9
2.1	9/2	Creating datasets from blank-delimited files (list input), permanent and temporary datasets, PROC CONTENTS, PROC PRINT, Viewtable	2.1-2.2, 2.4-2.5, 2.19-2.22, 4.4
2.2	9/4	Informats, infile options, column-oriented input, comments	2.6-2.8, 2.10-2.12, 2.14-2.15,
3.1	9/9	Formatted input, pointer control, MISSOVER / TRUNCOVER, adding passwords to datasets	2.9, 2.13
3.2	9/11	PROC IMPORT, PROC SQL, introduction to SQL, review of input methods, SET	2.3, 6.1-6.3
4.1	9/16	Creating new variables, IF statements, missing values, functions (beginning)	3.1-3.6
4.2	9/18	Functions (continued), converting between data types, random sampling, removing variable (KEEP / DROP) and records (OUTPUT / DELETE), outputting multiple datasets	3.7-3.8, 6.9, 6.11-6.12
5.1	9/23	Accessing values from a previous record (RETAIN, LAG), and dataflow diagrams	3.9
5.2	9/25	Using Procs to display and sort data, creating datasets from PROCs, FIRST and LAST	4.1-4.3, 4.9-4.11, 6.14
6.1	9/30	Arrays, variable-naming shortcuts, introduction to MERGE	3.10-3.11
6.2	10/2	MERGE	6.4-6.5
7.1	10/7	IN, UPDATE, user-defined formats, more system variables	6.8, 6.10
7.2	10/9	PUT, null data sets, system options, %INCLUDE	1.13, 4.5 – 4.8, 9.5
8.1	10/14	MACROs	Chapter 7
8.2	10/16	ODS, exporting data, PROC TRANSPOSE, and PROC COMPARE	1.10, Chapter 5, 6.13, Chapter 9
9.1	10/21	Example problems NOTE: CLASS IS IN L28-1307!!!	
9.2	10/23	Review	
10.1	10/28	EXAM	
10.2	10/30	No class	

Week	Date	Topics	Readings
11.1	11/4	DATABASE CLASS BEGINS: What is a database, data dictionaries, the relational model	
11.2	11/6	Relational model, continued	
12.1	11/11	Relational model, continued	
12.2	11/13	Security, transactions / roll back	
13.1	11/18	Forms design	
13.2	11/20	Views	
14.1	11/25	SQL for reporting, data migration, and subsetting	
14.2	11/27	THANKSGIVING, NO CLASS	
15.1	12/2	Stored procedures	
15.2	12/4	Review	
16.1	12/9	EXAM WEEK	

VI. Blackboard

- URL: https://blackboard.cudenver.edu
- Login & password = your 9-digit student ID (not SSN)
  - You can find your student ID number at https://hydra.cusys.edu/pinnacle/sishome1.hs.htm
  - Please change your password
- To download a document from a PC, right-click and choose Save As
- If you need help, email inquiry@cuonline.edu

VII. Accessing SAS

- To purchase it, go to Building 500, Room C4000. If you need directions, call x40400 or x44357
  - If you purchase it now, it will be good through June 30, 2009.
  - Cost is $115.
  - Pay by check, money order or IN. Bring a UCDenver student ID.
- Use it for free in certain computing labs: ED2 P28-2201C (13 systems) or RC1 P18-1309 (24 computers)

VIII. Honor Code:

Education at the Health Sciences Center is conducted under the honor system. All students who have entered health professional programs should have developed the qualities of honesty and integrity, and each student should apply these principles to his or her academic and subsequent professional career. All students are expected to have achieved a level of maturity, which is reflected in appropriate conduct at all times. All work done on exams or other assignments is to be done independently unless specific instruction to the contrary is provided.

APPENDIX C: Transcript

University of Colorado Denver, Anschutz Medical Campus
Student Admissions and Records

REPORT DATE: 03/30/2009

KATHLEEN CARROLL TORKKO
YOUR STUDENT NUMBER: XXX-XX-5050

COURSE TITLE	CRSE NR	HRS	GRADE	PNTS
------ FALL SEM 2008	UCD-ANSCHUTZ MEDICAL CAMPUS			------
NON-DEGREE	NONDEGREE PUBLIC HEALTH			
STAT ANLSY MICROARRY TEC	BIOS 6660	2.0	A	8.0
SAS DATABASE DESGN/MGMNT	BIOS 6680	3.0	A	12.0
ATT 5.0 EARNED 5.0	GPAHRS 5.0	GPAPTS 20.00	GPA 4.000	

*** END OF ACADEMIC RECORD ***

APPENDIX D: Syllabus for Course Taught (HSBC 4001/5001 Introduction to Epidemiology, Spring 2008)

UNIVERSITY OF COLORADO AT DENVER AND HEALTH SCIENCES CENTER COLLEGE OF LIBERAL ARTS & SCIENCES

HBSC 4001 / 5001: INTRODUCTION TO EPIDEMIOLOGY

Term: Spring 2008
Course dates/times: Tuesdays, 4-6:50 p.m.

Course location: (WC)159
Office Hours: By appointment 1 hour before class
Administration Building 255B

Professor: Kathleen C. Torkko, PhD, MSPH
Office location: Anschutz Medical Campus
RC1-North, Room P18-5120
Phone: 303-724-3063
Email address: kathleen.torkko@uchsc.edu
Web site and/or BlackBoard site

Catalogue Description (HBSC 5001):

Introduces the basic concepts of public health and epidemiology, including assessment of disease in the community, the study of causation and association of disease with lifestyle and environmental risk factors, as well as related special topics. Prereq: upper division standing and course in basic statistical methods. Cross-listed with HBSC 4001.

Instructor Description:

This is an introductory epidemiology course designed for graduate students in the Health and Behavioral Sciences (HBS) program at the University of Colorado Denver. The model for this course is the Introduction to Epidemiology (PRMD 6630) taught in the Department of Preventive Medicine and Biometrics (PMD) at the Health Sciences Center campus. This course will cover the same basic epidemiologic concepts taught in that class allowing students to take advanced epidemiology courses taught through PMD. Because epidemiology is considered part of the medical sciences and its roots come from the study of infectious disease, it is necessary to discuss the medical aspects of disease to illustrate many epidemiologic principles. It will also be necessary for students to brush up on their basic math skills. Content for this course will include some emphasis on topics that may be of more interests to HBS students as compared to the more purely medical focus of the 6630 course.

This course will provide students with an understanding of the basic methods and tools used by epidemiologists to study rates and risks for disease and other factors that affect the health of people. Epidemiologic techniques are used to study a wide variety of health concerns including infectious disease outbreaks, risk factors for chronic diseases, and societal and behavioral factors affecting access to and use of health services. This variety makes epidemiology an exciting and useful area of study. Although this course will not turn you into epidemiologists, I hope you will develop some excitement for the subject and an appreciation for the relevance of epidemiology to your areas of interest.

Epidemiology is not black-and-white. Often there is not necessarily a “right” answer. There may be many ways to study a problem and the choice of an approach will depend on the nature of the questions being asked and on such practicalities as the availability of data and costs. Sometimes we choose the best answer or one way to study a problem, although it is not necessarily the only answer nor the only way to study it. Epidemiology is often a science of compromises. This can be particularly aggravating for students who might prefer that all questions have either right or wrong answers. All this can make epidemiology a difficult subject to teach and to learn. It is possible that you may pose questions that I am not able to answer immediately, or I may change my mind after further reflection. I also expect that some of you will come up with answers that had not occurred to me. I anticipate a dialog between you and myself. Please feel free to ask questions. I look forward to teaching and learning from you.

One theme for this class is the use of epidemiologic techniques to study health disparities in populations. You will be expected to complete a final project consisting of a short paper using what was learned over the semester to describe a health disparity whether by race, gender, age, geography, socioeconomic status or other factors of interest. I have a grant to study health disparities in cancer, particularly in prostate cancer. This is a wonderful opportunity for students to teach the teacher about health disparities, particularly in prostate cancer.

To learn epidemiology, a student may need several passes through the material. It is expected that you will have read all materials and performed all tasks assigned for a particular session prior to the start of class. Reading the material in advance will help you formulate questions. My teaching style will be interactive with in-class

exercises and self-assessments to facilitate in-class discussion to help me gauge now well students are learning (and how well I am explaining things!).

Because we are meeting for 3 hours, the class session will be divided into two sub-sessions, A and B, with a short break in between depending on time constraints for a particular lecture. Each session will include two separate lectures on related topics or a lecture with an in-class exercise. Much of the in-class work will require some preparation that will serve as the homework for the (sub-)session.

Handouts of the lecture slides will be posted at least 24 hours prior to each lecture so you may print them for lecture notes. Materials will be accessible on Blackboard. I will be available before each session for questions and additional help. I will try to arrive at least 30-60 minutes prior to each class session (I am a person who is usually running late!). I can make it earlier to class by appointment. Please feel free to e-mail me or call.

Course Objectives:

At the end of this course, the student will:

1. Be able to use epidemiologic terminology
2. Understand and calculate different rates and measures of association (*i.e.*, OR, RR)
3. Articulate clearly the strengths and limitations of different epidemiologic study designs
4. Understand important epidemiologic concepts including confounding, bias, and causation
5. Be able to critically read epidemiologic literature to recognize study design and analytical strengths and limitations.

Required Text:

Gordis L. Epidemiology, 3rd Ed., Elsevier Saunders, 2004

Assignments:

Homework: Generally homework will be assigned for each sub-session. This includes working out problems, providing short answers and definitions, and reading assignments. The homework assigned will usually cover material that will be discussed at the session. Although this may seem counter-intuitive, grappling with problems and deriving your own solutions before learning how other people have done it will give you experience in solving new problems and allow you to develop a clearer view of the strengths and weaknesses of accepted solutions. Try working out problems first by yourself. If you run into difficulty, feel free to collaborate with your fellow students. But don't just copy answers. If you really don't understand something, discuss it or contact me. Homework must be submitted prior to class electronically or on hard copy at the beginning of class. Failure to do so will deduct 20% from your score (unless you have an EXCELLENT reason for being late). Graded assignments will be returned the next class session. Answers to homework will be posted on Blackboard a week after they are due.

Exams: There will be two formal exams, a midterm (on March 11) and a final (on May 12). The exams will be in-class and open book and will include multiple choice questions and short answers. Some calculations will be required so calculators will be permitted, but not computers. The midterm will cover material presented up to that point; the final will cover the entire term with an emphasis on the latter half. There will be opportunities for formal review before each exam. The first hour of the session will be given to any review questions with the latter 2 hours for the exam.

A final project will entail writing a 3-5 page paper (double-spaced) plus tables or figures. The topic will be of your choice but must cover a health disparity in Colorado, the US, or elsewhere around the world. The topic must be OK'd by me (topic must be chosen by April 1). Preference should be given to cancer, particularly prostate cancer, or another topic that is of great interest to you or your work. There will be no preferential grading given to those who pick prostate cancer, so you are free to choose as you wish. If you can't decide on a topic, I will assign one to you. For this project you will use epidemiology to describe the disparity (rates, risks, etc.) and discuss the types of studies, source of data to describe the disparity. You will briefly discuss any potential problems with the data or gaps in our knowledge. We will discuss the requirements in more detail during a class session. The paper must be submitted electronically or on hard copy by May 6.

Graded midterms will be returned the following class session. Graded final exams and projects will be available at the HBS office after May 19th.

Grades:

Final grades will be determined on a curve and based on homework assignments, in-class exercises, two exams (midterm and final), and a final project according to the following distribution:

Homework	15 %
In-class exercises	15 %
Midterm Exam	25 %
Final Exam	25 %
Final Project	20 %
Total	100%

In-class participation will also be assessed by awarding additional points based on a scale from 0-10 with "0" meaning you never opened your mouth in class to 10 meaning you participated in most if not all discussions. This means a total score of 110 points is possible, but remember, the class is graded on a curve.

Course Policies:

Class attendance and participation is essential for success. No deductions in the final grade will be applied for non-attendance (as long as assignments are turned in on time), but you will miss out on critical questions and discussions. There is no requirement to notify me if you miss class, but I would appreciate a courtesy e-mail to explain unanticipated absences.

The schedule of coursework listed below is not written in stone and may be subject to unplanned changes such as instructor or guest lecturer illness. Additionally, I reserve the right to change the syllabus depending on the needs and interests of the students. Students will be given appropriate, timely, and written notification of any changes.

Homework can either be (clearly) handwritten or typed with room in the margins for me to make comments. Homework can be submitted electronically (MS-Word) or on hard copy. When students' work conveys that they require additional help in composition or math, students will be referred to the Writing Lab and/or the Math Lab. It is your responsibility to clarify missed assignments with me. Homework not submitted in time (by the beginning of the class session) will have a 20% reduction applied to the score. Late homework not submitted by or at the beginning of the following class session will not be graded (although you will get feedback).

If you will miss a scheduled exam, you must notify me prior to the start of the exam. In cases of an emergency, you can call me on my cell phone or contact the HBS office to leave a message. A make-up exam will be re-scheduled. This should be done within a week after the date of the original exam. This may mean you will have to travel to the Anschutz Medical Campus to take the exam unless I can find someone to proctor it on the Auraria Campus. If a make-up is necessary, I ask the other students to refrain from sharing any specific information about the content of the exam with the student(s) who will be taking the make-up.

Course Schedule:

Date	Topic	Required Reading*	Assignments
01/22/08 A	Introduction, Course Requirements		
01/22/08 B	Introduction to Epidemiology	Gordis Chapt 1	None due
01/29/08 A	Measures of Health Status	Gordis Chapt 3 (pp 32-33; 42-46) Chapt 4 (pp 48-58)	Homework 1
01/29/08 B	Incidence & Prevalence	Gordis Chapt 4 (p 48-58)	Homework 2
02/05/08 A	Rate Adjustment & Attributable Risk	Gordis Chapt 4 (pp 58-70) Chapt 12	Homework 3
02/05/08 B	In-class Exercise	Exercise 1	Exercise 1
02/12/08 A	Cohort Studies & Relative Risk	Gordis Chapt 9, Chapt 11 (pp 177-81); *Scand J Pub Health* 2007;35:306-12.	Homework 4
02/12/08 B	Case-Control Studies & Odds Ratios	Gordis Chapt 10, Chapt 11 (pp 181-88);	Homework 5
02/19/08 A	Other Observational Study Designs / Causation	Gordis Chapt 14	Homework 6
02/19/08 B	In-class Exercise	Exercise 2	Exercise 2
02/26/08 A	Clinical Trials & Prognosis	Gordis Chapt 6, 7, 8	Homework 7

02/26/08 B	In-class Exercise	Exercise 3	Exercise 3
03/04/08 A	Natural History of Disease / Levels of Prevention	Gordis Chapt 2	Homework 8
03/04/08 B	In-class Exercise	Exercise 4	Exercise 4
03/11/08 A	Review questions		
03/11/08 B	MIDTERM EXAM		
03/18/08 A	Bias, Confounding & Effect Modification	Gordis Chapt 15. *Scand J Pub Health* 2007;35:306	Homework 9
03/18/08 B	In-class Exercise	Exercise 5	Exercise 5
03/25/08	SPRING BREAK – no class		
04/01/08 A	Screening Tests: Sensitivity, Specificity, etc.	Gordis Chapt 5, 18	Homework 10
04/01/08 B	In-class Exercise	Exercise 6	Exercise 6
04/08/08 A	Guest Lecture: Using GIS in Epidemiology - Thomas	*Environmental Health Perspectives* 2004;112:998-1006	TBA
04/08/08 B	Prostate Cancer Epidemiology; Discussion of Final Health Disparities Project	*Cancer* 2007;110:1889-99.	Homwork 11
04/15/08 A	Guest Lecture: Health Disparities in Tobacco Burden – Levinson	TBA	TBA
04/15/08 B	Epidemiology of Health Disparities	*J Transcult Nurs* 2008;19:83-91.	Homework 12
04/22/08 A	Guest Lecture: Lifecourse Epidemiology - Dablea	*Ann Rev Pub Health* 2005;26:1-25	TBA
04/22/08 B	Guest Lecture: Community Epidemiology – Baxter	TBA	TBA
04/29/08 A	Guest Lecture: Sun Protection in Children – Crane	TBA	TBA
04/29/08 B	Criticism of Epidemiology: Hormone Replacement Therapy and Heart Disease in Women	Do We Really Know What Makes Us Healthy? By Gary Taubes, The Times Magazine, 9/16/07	Homework 13
05/06/08 A	Ethics & Human Subject Research	Gordis Chapt 20	Homework 14
05/06/08 B	In-class Exercise	Exercise 7	Exercise 7
05/13/08 A	Review Session		
05/13/08 B	FINAL EXAM		

*Lists for other reading assignments (pertinent papers, etc.) will be available the first day of class or throughout the course before specific classes.

APPENDIX E: April 15, 2009 Lecture on Health Disparities for Introductory Epidemiology Class

(see next page)

Session 12B 04/15/08

Health Disparities

Kathleen C. Torkko, PhD, MSPH, MS

Departments of Preventive Medicine and Biometrics, and Pathology
University of Colorado Denver, Anschutz Medical Campus

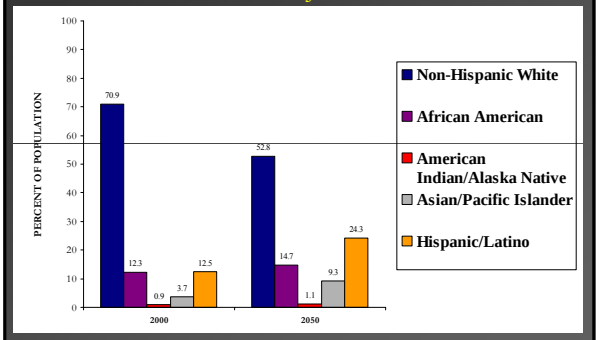
"Nowhere are the divisions of race and ethnicity more sharply drawn than in the health of our people…"

President Bill Clinton

"Of all the forms of inequality, injustice in health is the most shocking and the most inhumane."

Martin Luther King Jr.

Population by Race & Hispanic Origin: United States, 2000 & Projected 2050



U.S. Census Bureau

What are Health Disparities?

Differences in
- rates of diseases
- health outcomes
- health care access
- medical treatment

affecting the health status of different groups

What are Health Disparities?

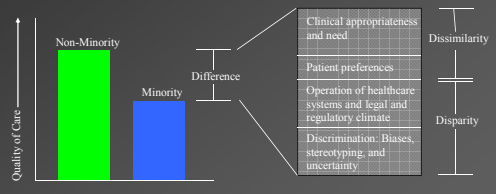
The variation in physical, mental, or social well-being based upon gender or race/ethnicity, insurance status, treatment differences, disability, stigma, etc.

Achieving equity in health implies eliminating inequalities between social groups which are unnecessary, avoidable and therefore unjust.

Often spoken of in terms of race-ethnicity, but disparities also exist by gender, age, socio-economic status, place of residence (rural vs. urban), etc.

Model of Health Care Disparities

The model views health care disparities as resulting from characteristics of the health care system, the society's legal and regulatory climate, discrimination, bias, stereotyping and uncertainty. Not all dissimilarities in care are necessarily a disparity.



Gomes, C. and McGuire T.G. 2001. Identifying the sources of racial and ethnic disparities in health care use. Unpublished manuscript cited in: IOM,. 2002. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care.*

What is a Health Disparity?

Lack of equality as of opportunity, treatment, or status

Inequity

- Unfair and unjust
- Unnecessary and avoidable

Communities of color are disproportionately affected

Inequity in Health/ Health Disparity

In Health Status

Different groups (*e.g.*, women and men, racial/ethnic groups) have unequal opportunities to enjoy good health, and become ill or dying through causes that are unjust and avoidable.

- Patient-level factors – including patient preferences, refusal of treatment, poor adherence, biological differences

Does not mean just unequal rates of mortality or morbidity for each group

In Health Care (access/use)

Differential distribution and access to resources (technological, financial, human) not according to need

- Health systems-level factors – financing, structure of care; cultural and linguistic barriers

Potential Sources of Racial and Ethnic Health Disparities – Healthcare Systems-level Factors

Cultural and linguistic barriers – many non-English speaking patients report having difficulty accessing appropriate translation services

Lack of stable relationships with primary care providers – minority patients, even when insured at the same level as whites, are more likely to receive care in emergency rooms and have less access to private physicians

Financial incentives to limit services – may disproportionately and negatively affect minorities

IOM

Potential Sources of Health Disparities: Stereotyping

Stereotyping can be defined as the process by which people use social categories (*e.g.*, race=racism, sex=sexism) in acquiring, processing, and recalling information about others.

According to a study done by Ryan and Burke (2000), doctors rated black patients as less intelligent, less educated, more likely to abuse drugs and alcohol, to fail to comply with medical advice, to lack social support, and less likely to participate in cardiac rehabilitation than white patients, even after patients' income, education, and personality characteristics were taken into account

IOM

Unequal Treatment

In 2003 the Institute of Medicine (IOM) published *Unequal Treatment* which compiled research demonstrating substantial racial and ethnic variation in quality of health care.

Unequal Treatment brought healthcare disparities to the attention of the nation, placing the issue on the forefront of the nation's health policy agenda.

Unequal Treatment: Study Goals

Assess the extent of racial and ethnic differences in healthcare that are not otherwise attributable to known factors such as access to care (*e.g.*, ability to pay or insurance coverage);

Evaluate potential sources of racial and ethnic disparities in healthcare, including the role of bias, discrimination, and stereotyping at the individual (provider and patient), institutional, and health system levels; and,

Provide recommendations regarding interventions to eliminate healthcare disparities.

Media Response to *Unequal Treatment*

USA Today, March 22, 2002, "Racial Bias in Health Care"

"In unassailable terms, the report found that even when their insurance and income are the same as those of whites, minorities often receive fewer tests and less sophisticated treatment for a panoply of ailments, including heart disease, cancer, diabetes and HIV/AIDS. By stripping away the pretense that the differences can be explained by minorities' lack of access to timely care, the report should spur doctors and patients to question why racial disparities are tolerated in medicine."

Dimensions of Health Disparities

- Language Barriers
- Access Barriers
- Economic, Poverty Barriers
- Cultural Barriers
- Distrust Barriers
- Policy Barriers
- Stereotyping Barriers

Socio-economic status (SES) remains perhaps the most powerful force producing health disparities – it is multi-factorial and complex

Health Disparities/Inequalities

Insurance access:
- Availability, affordability: lower levels of insurance coverage among low SES individuals,
- Acceptability: different use of care by different social groups (*e.g.*, gender, language and cultural barriers, discrimination based on stereotypes); distrust of system

SES**:** income equity, education, family structure (support). As SES rises, health improves.

Gender: gender differences by ethnicity, income, and education manifest themselves in mortality and health rates.

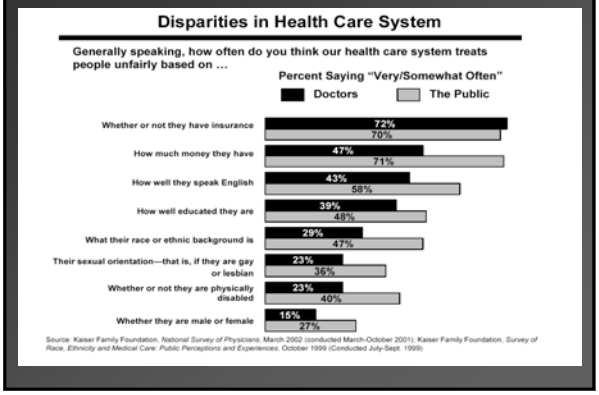
Race/Ethnicity: differential mortality and health rates by ethnic groups

Consequences of Being Uninsured

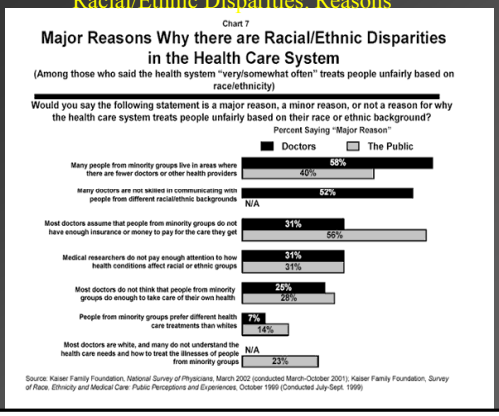
- Use fewer preventive and screening services
- Are sicker when diagnosed
- Receive fewer therapeutic services
- Have poorer health outcomes (higher mortality and disability rates)
- Have lower annual earnings because of poorer health

Source: Hadley, Jack. Sicker and Poorer-the consequences of being uninsured. *Medical Care Research and Review*, 60(2). 2003

Stereotyping/Discrimination



Racial/Ethnic Disparities: Reasons



Evidence of Racial and Ethnic Disparities in Healthcare

- Disparities consistently found across a wide range of disease areas and clinical services
- Disparities are found even when clinical factors, such as stage of disease presentation, co-morbidities, age, and severity of disease are taken into account
- Disparities are found across a range of clinical settings, including public and private hospitals, teaching and non-teaching hospitals, etc.
- Disparities in care are associated with higher mortality among minorities

IOM

Health Disparities Facts

Infant Mortality Rates for black babies remain nearly two-and-one-half times higher than for whites

Life Expectancy for black men and women remains at nearly one decade fewer years of life compared with whites

Rates Of Death attributable to heart disease, stroke, prostate and breast cancer remain much higher in black populations.

Diabetes Rates are more than 30% higher among Native Americans and Hispanics than among whites.

Minorities remain grossly under-represented in the health profession workforce relative to their population proportions

Source: Addressing Ethnic and Health Disparities. Centers for Disease Control and Prevention, 2001.

Examples of Health Disparities

Differences in rates of disease

Blacks and American Indians have diabetes at higher rates than Whites

Differences in outcomes of disease

Compared to Whites, a higher percentage of Black and Native American babies die in the first year of life

Black women die of cervical cancer at twice the rate of White women

Differences in access/treatment

In one study -- Minority nursing home patients were less likely than White patients to receive medicine for their pain

Racial minorities are less likely than Whites to receive certain cardiac diagnostic procedures

Health Care Disparities

A study of the U.S. national cancer registry (SEER) found that:

African-American and Hispanic men received had longer time intervals between diagnosis and receipt of medical monitoring visit.

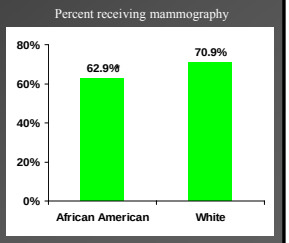
Nearly 6% of African-American men and 5% of Hispanic men as compared to 1% of white men did not have any medical monitoring visits or procedures during the 60-month follow up period.

Source: Shavers VL, Brown ML, Klabunde CN, Potosky AL, Davis WW, Moul JW, Fahey A. "Race/ethnicity and the intensity of medical monitoring under 'watchful waiting' for prostate cancer. Medical Care, March 2004, 42 (3):239-250

N=49901, p<0.001

Health Care Disparity

Among patients in Medicare managed care (age 65 for older), African-American patients are less likely than white patients to receive breast cancer screening (mammogram).

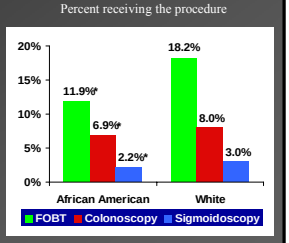


Source: Schneider EC, Zaslavsky AM, Epstein AM. Racial disparities in the quality of care for enrollees in Medicare managed care. JAMA. 2002 Mar 13;287(10):1288-94.

* Statistically significant difference between African Americans and whites.

Health Care Disparity

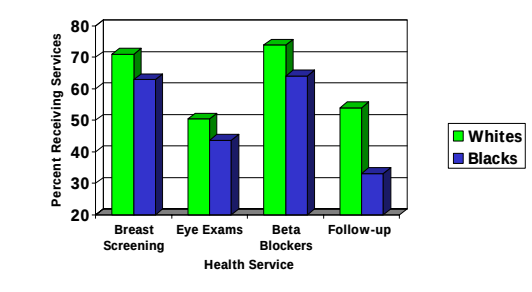
In a study of race differences in the use of three cancer screening procedures among Medicare patients (age 65 for older), African-American patients are less likely than white patients to receive each procedure.



Source: Cooper GS Koroukian SM "Racial disparities in the use of and indications for colorectal procedures in Medicare beneficiaries" Cancer. 2004 Jan 15;100(2):418-24.

* Statistically significant difference between African Americans and whites all categories.

Among Medicare Beneficiaries Enrolled in Managed Care Plans, African Americans Receive Poorer Quality of Care (Schneider et al., *JAMA*, March 13, 2002)



IOM

Racial/Ethnic Disparities: Cancer

- Black men and women have a 20% to 40% higher death rate from cancer than white men and women.
- American Indian/Alaskan Native, Asian/Pacific Islander and Hispanic populations have lower overall cancer incidence and death rates.
- Non-black minority groups have a higher incidence of stomach, liver and cervical cancers.
- Racial and ethnic minority groups are also more likely to present with advanced stage cancers.

Burden of Cancer in the US

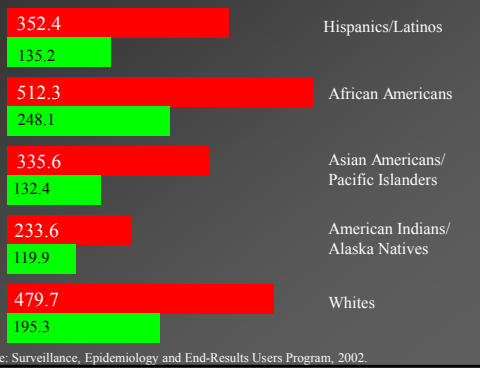
Hispanics have the highest cervical cancer incidence rates:
- 15.8 per 100,000 Hispanic females
- Almost twice the incidence rate of White females

African Americans have the highest prostate cancer mortality rates:
- 68.1 deaths per 100,000 black men
- More than twice the rate of whites and nearly three times the rate of Hispanics

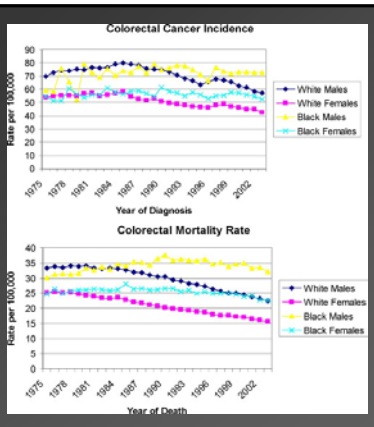
Asian Americans/Pacific Islanders have the highest incidence rates of liver and stomach cancers for both genders:
- 14.0 per 100,000 for liver and bile duct cancer– more than twice as high as any other population group
- 15.9 per 100,000 for stomach cancer, which is twice the incidence rate for Whites

Overall Cancer Disparities

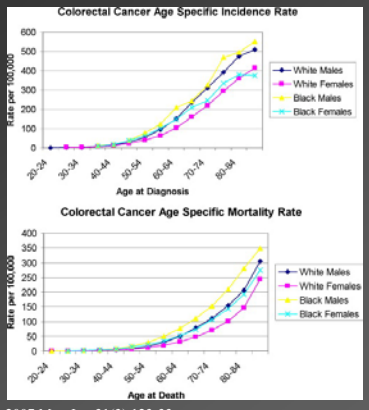
Cancer Incidence and Mortality (per 100,000)



Source: Surveillance, Epidemiology and End-Results Users Program, 2002.

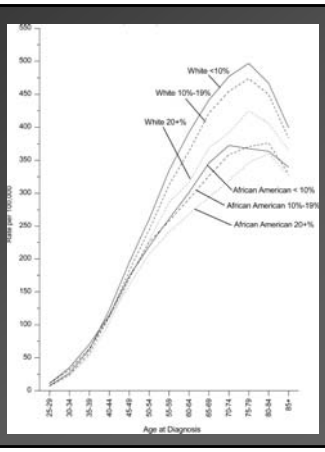


Curr Probl Cancer. 2007 May-Jun;31(3):123-33



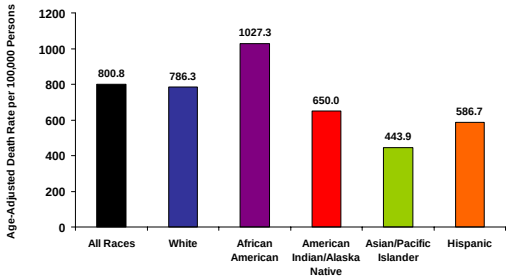
Curr Probl Cancer. 2007 May-Jun;31(3):123-33

Age-Specific Female Breast Cancer Incidence Rates by Race and County Poverty Level, US, 1998-2002



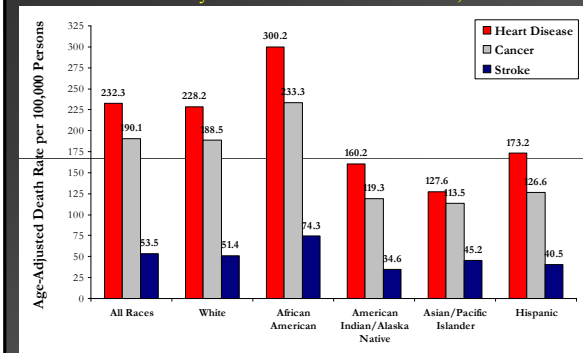
From Smigal, C. et al.
CA Cancer J Clin 2006;56:168-183.

Age-Adjusted Death Rates per 100,000 Persons by Race and Hispanic Origin for All Causes: U.S., 2004



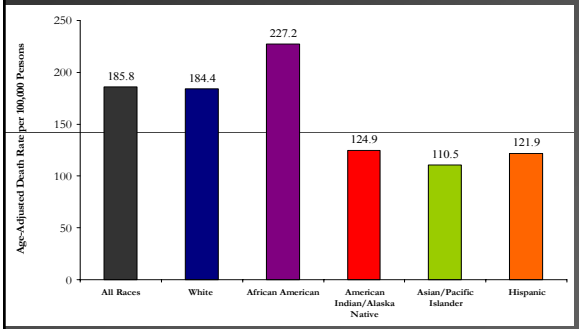
www.cdc.gov

Age-Adjusted Mortality Rates per 100,000 Persons by Race/Ethnicity for 3 Health Focus Areas: U.S., 2003



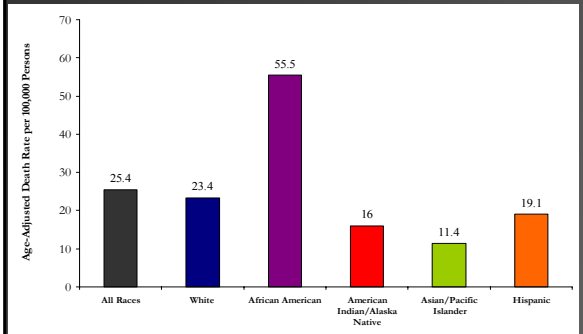
www.cdc.gov

Age-adjusted Mortality Rates Per 100,000 Persons By Race/Ethnicity For Malignant Neoplasms: U.S., 2004.



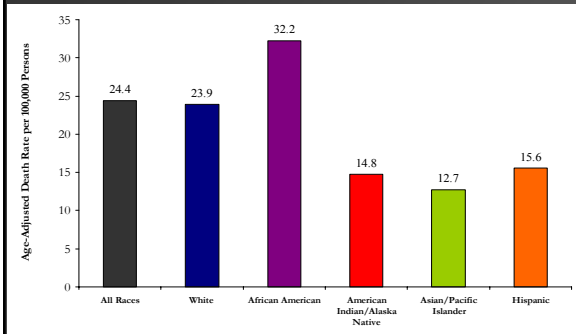
www.cdc.gov

Age-adjusted Mortality Rates Per 100,000 Persons By Race/Ethnicity For Prostate Cancer: U.S., 2004.



www.cdc.gov

Age-adjusted Mortality Rates Per 100,000 Persons By Race/Ethnicity For Breast Cancer: U.S., 2004.



www.cdc.gov

Racial Disparities in Cancer Therapy

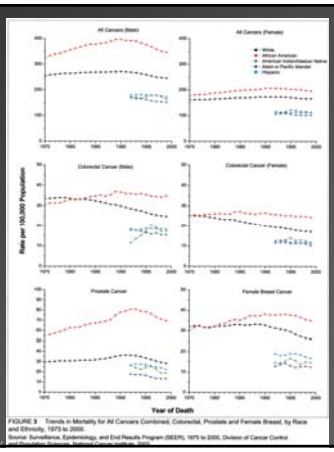
Cancer type & stage	Therapy	% of Patients receiving therapy		Relative risk of receiving therapy (black vs white)	
		Black	White	Crude	Adjusted
Early stage breast (lumpectomy)	Radiation	77.8	85.8	0.91 (0.87, 0.94)	0.93 (0.90, 0.96)
Late stage breast	Chemotherapy	52.0	53.3	0.98 (0.86, 1.09)	0.99 (0.84, 1.13)
Early stage lung	Resection	64.0	78.5	0.82 (0.77, 0.86)	0.81 (0.76, 0.87)
Late stage colon	Chemotherapy	52.1	64.1	0.81 (0.75, 0.87)	0.76 (0.68, 0.83)
Late stage rectum	Radiation+chemo	35.2	48.9	0.72 (0.57, 0.89)	0.73 (0.55, 0.92)

Cancer 2008; Published online 1/7/08

Racial/Ethnic Disparities: Cancer

Source: U.S. Cancer Statistics Working Group. 2005

GENDER	INCIDENCE RATE (per 100,000)	DEATH RATE (per 100,000)
MEN	blacks (615.1) Whites (536.8) Hispanics (422.8) Asians/Pacific Islanders (324.3) American Indians/Alaska Nat.(267.2).	Blacks (322.9) Whites (236.0) Hispanics (163.9) American Indians/Alaska Nat. (145.3) Asians/Pacific Islanders (138.8)
WOMEN	Whites (408.9) Blacks (377.5) Hispanics (310.4) Asians/Pacific Islanders (264.5) American Indians/Alaska Nat. (215.4).	Blacks (190.9) Whites (161.9) American Indians/Alaska Nat. (114.5) Hispanics (107.4) Asians/Pacific Islanders (96.6).
BY ETHNIC GROUP	American Indian/Alaska Native men: lowest cancer incidence rate White women: highest incidence rates American Indian/Alaska Native women: lowest cancer incidence and the third-highest cancer death rates.	Black women: highest cancer death rates



From Ward, E. et al.
CA Cancer J Clin 2004;54:78-93.

Disparities in Diagnostic Care

The length of time between an abnormal screening mammogram and the follow-up diagnostic test to determine whether a woman has breast cancer is more than twice as long for Asian American, black, and Hispanic women as for white women.

(Source: CDC/ Agency for Healthcare Research and Quality)

Unequal Treatment: Summary of Findings

Racial and ethnic disparities in health care exist and, because they are associated with worse outcomes in many cases, are unacceptable.

Racial and ethnic disparities in health care occur in the context of broader historic and contemporary social and economic inequality, and evidence of *persistent* racial and ethnic discrimination in many sectors of American life.

Many sources – including health systems, health care providers, patients, and utilization managers – contribute to racial and ethnic disparities in health care

IOM

Unequal Treatment: Summary of Findings – cont.

Bias, stereotyping, prejudice, and clinical uncertainty on the part of healthcare providers may contribute to racial and ethnic disparities in healthcare. While indirect evidence from several lines of research supports this statement, a greater understanding of the prevalence and influence of these processes is needed and should be sought through research.

Racial and ethnic minority patients are more likely than white patients to refuse treatment, but differences in refusal rates are generally small, and minority patient refusal does not fully explain healthcare disparities.

IOM

Summary of Recommendations

General Recommendations

Increase awareness of racial and ethnic disparities in health care among the general public and key stakeholders, and increase health care providers' awareness of disparities.

Legal, Regulatory, and Policy Recommendations

Avoid fragmentation of health plans along socioeconomic lines, and take measures to strengthen the stability of patient-provider relationships in publicly funded health plans

IOM

Legal, Regulatory, And Policy Recommendations (Continued)

Increase in the proportion of underrepresented U.S. racial and ethnic minorities among health professionals;

Apply the same managed care protections to publicly funded HMO enrollees that apply to private HMO enrollees;

Provide greater resources to the U.S. DHHS Office of Civil Rights to enforce civil rights laws.

IOM

Caveats – *Unequal Treatment*

Access (e.g., insurance status, ability to pay for healthcare) is *the* most important predictor of the quality of healthcare across racial and ethnic groups

It is difficult – even artificial – to separate access-related factors from social categories such as race and ethnicity

The bulk of research on healthcare disparities has focused on black-white differences – more research is needed to understand disparities among other racial and ethnic minority groups

IOM

Office of Minority Health and Health Disparities (OMHD)

Centers for Disease Control & Prevention (CDC)

OMHD aims to eliminate health disparities for vulnerable populations as defined by race/ethnicity, socio-economic status, geography, gender, age, disability status, risk status related to sex and gender, and among other populations identified to be at-risk for health disparities.

OMHD Critical Goals

Equity in health impact

Diversity in customer focus

Access to and participation in public health systems

Participation in the conduct and use of public health research to solve community wide health problems

The benefits of global health protection, especially among immigrants and border populations

A verifiable commitment to operational efficiency, program effectiveness, and accountability for public resources.

CRCHD.cancer.org
Center to Reduce cancer health disparities; NIH

www.healthypeople.gov

Addressing Health Disparities

GOALS:

Increase Quality and Years of Healthy Life
Eliminate Health Disparities

www.healthypeople.gov

Webpage links to over 20 HHS health disparities initiatives:
http://www.hhs.gov/ocr/healthdisparities.html

Healthy People 2010 Is Designed To Achieve Two Overarching Goals

Goal 1: Increase Quality and Years of Healthy Life

The first goal of Healthy People 2010 is to help individuals of all ages increase life expectancy *and* improve their quality of life.

Goal 2: Eliminate Health Disparities

The second goal of Healthy People 2010 is to eliminate health disparities among different segments of the population.

Achieving Equity in Health

Eliminating avoidable and unfair differences between groups in health status & survival

Allocating resources & providing access to quality health care according to the special needs of different groups

Each person paying for health care according to their economic capacity, not their need

Making justice for people in the social distribution of responsibilities, power & rewards for their contribution to health production

APPENDIX F: Sociodemographic survey
(see next page)

SAN ANTONIO CENTER OF BIOMARKERS OF RISK FOR PROSTATE CANCER
SABOR

Phone: 210-567-0214 • 1-800-335-4594 • Email: upr@uthscsa.edu

Mm/dd/yyyy
SABOR #

{FirstName LastName}
{Address}
{City, State Zipcode}

Dear Mr. {LastName}

We would like to express our appreciation for your support and participation in the SABOR prostate study. We now want to ask for some additional information that will help us look at other risk factors that may play a roll in the progression of prostate cancer. If we are sending this letter to you by mistake, please contact us so that we can correct our records. If we have not seen you within the past 12 months, please call us to set up an appointment.

We'd like to begin by making sure that we have collected all of the information about you and your prostate health to date. Please take a moment to help us be sure our information is correct.

1. Have you had a prostate biopsy before? ☐ Yes ☐ No

   If you have had one or more prostate biopsies before, can you please tell us when and where?

Year	Location where biopsy performed	Biopsy result (normal or cancer)
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

2. If you have been diagnosed with prostate cancer, please tell us the treatment you selected first after your prostate cancer diagnosis (within 6 months of your prostate cancer diagnosis).
   - ☐ Surgery (radical prostatectomy). Hospital where performed:_____
   - ☐ External beam radiation
   - ☐ Brachytherapy (placement of radioactive seeds into the prostate)
   - ☐ None (watchful waiting or active surveillance)
   - ☐ Hormone therapy (medications or treatments to lower testosterone levels)
   - ☐ Other. Please tell us what treatment you had:_____

3. Have you had any additional treatments *after six months* following your diagnosis?

- ☐ Surgery (radical prostatectomy). Hospital where performed: _____
- ☐ External beam radiation
- ☐ Brachytherapy (placement of radioactive seeds into the prostate)
- ☐ None (watchful waiting or active surveillance)
- ☐ Hormone therapy (medications or treatments to lower testosterone levels)
- ☐ Other. Please tell us what treatment you had:_____

4. Were you born in the United States? ☐ Yes ☐ No

5. If you were born outside the United States, in what year did you come to the US? _____

6. How long have you lived in the San Antonio area?

☐ less than 1 year ☐ 1-2 years ☐ 2-5 years ☐ 5-10 years ☐ more than 10 years

7. Are you? ☐ Married ☐ Divorced ☐ Widowed
☐ Never married ☐ Separated ☐ Living with a partner

8. What is the higher grade or year of school you completed?

- ☐ less than 12 years (did not graduate from high school)
- ☐ Grade 12 or GED (high school graduate)
- ☐ College for 1-3 years (some college or technical school)
- ☐ College 4 years (or more; college graduate)
- ☐ Graduate school

9. How comfortable are you speaking English?

- ☐ Completely comfortable (English is my native language)
- ☐ Very comfortable
- ☐ Somewhat comfortable
- ☐ Not at all comfortable

10. Are you currently? ☐ Employed for wages ☐ Self-employed ☐ Unemployed
☐ Retired ☐Disabled

11. What is (was) your main occupation? _____

12. Do (Did) you primarily work indoors or outdoors? ☐ Indoors ☐ Outdoors

13. What is your current annual household income from all sources?

☐ Less than $15,000 ☐ $15,001 to $30,000 ☐ $30,001 to $50,000
☐ $50,001 to $75,000 ☐ $75,001 to $100,000 ☐ More than $100,000

14. Do you currently rent or own your home?

☐Rent ☐ Own ☐ Live in house/apartment but do no have to pay rent

15. Would you say that in general you health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

16. Do you have any kind of health care coverage, including health insurance, prepaid plans (like HMOs), or government plans (like Medicare)? ☐ Yes ☐ No ☐ Not sure

17. How many hours do you usually exercise (walking, running, playing sports, etc) each week?

☐ Less than 1 hour ☐ 1 to 2 hours ☐ 3 to 4 hours ☐ More than 4 hours

18. How likely do you think it is that you will develop prostate cancer in the future?

☐ Very low ☐ Somewhat low ☐ Moderate ☐ Somewhat high ☐ Very high

19. How often do you worry about getting prostate cancer?

☐ Rarely or never ☐ Sometimes ☐ Often ☐ All the time

PLEASE PUT BOTH PAGES IN THE ADDRESSED ENVELOPE PROVIDED. IF YOU HAVE ANY QUESTIONS, PLEASE FEEL FREE TO GIVE US A CALL.

APPENDIX G: List of Single Nucleotide Polymorphisms

SNP_Name	Chromosome	Gene
rs9332975	2	SRD5A2
rs2268794	2	SRD5A2
rs2268796	2	SRD5A2
rs2208532	2	SRD5A2
rs4952222	2	SRD5A2
rs632148	2	SRD5A2
rs3754838	2	SRD5A2
rs9332960	2	SRD5A2
rs12721364	12	VDR
rs9729	12	VDR
rs739837	12	VDR
rs11168267	12	VDR
rs11574077	12	VDR
rs2239182	12	VDR
rs2107301	12	VDR
rs2239179	12	VDR
rs12717991	12	VDR
rs12721370	12	VDR
rs2189480	12	VDR
rs3819545	12	VDR
rs3782905	12	VDR
rs2239186	12	VDR
rs2254210	12	VDR
rs2238136	12	VDR
rs4760648	12	VDR
rs11168287	12	VDR
rs4328262	12	VDR
rs4237855	12	VDR
rs11574026	12	VDR
rs7302235	12	VDR
rs12581281	12	VDR
rs4516035	12	VDR
rs7139166	12	VDR
rs1048691	12	CYP27B1
rs4646537	12	CYP27B1
rs8176345	12	CYP27B1
rs703842	12	CYP27B1
rs4646536	12	CYP27B1
rs2762929	20	CYP24A1
rs8118441	20	CYP24A1
rs6068810	20	CYP24A1
rs6097807	20	CYP24A1
rs2762934	20	CYP24A1
rs1570669	20	CYP24A1
rs2296239	20	CYP24A1
rs6068816	20	CYP24A1
rs4809958	20	CYP24A1
rs3787554	20	CYP24A1
rs2244719	20	CYP24A1
rs2762941	20	CYP24A1
rs2181874	20	CYP24A1
rs4809960	20	CYP24A1
rs2296241	20	CYP24A1

SNP_Name	Chromosome	Gene
rs2245153	20	CYP24A1
rs2585428	20	CYP24A1
rs13038432	20	CYP24A1
rs6022999	20	CYP24A1
rs2248359	20	CYP24A1
rs4809957	20	CYP24A1
rs1059519	19	PDF/GDF15
rs1059369	19	PDF/GDF15
rs1804826	19	PDF/GDF15
rs16982345	19	PDF/GDF15
rs1227733	19	PDF/GDF15
rs1491711	4	GC/VDBP
rs17383291	4	GC/VDBP
rs705117	4	GC/VDBP
rs2282679	4	GC/VDBP
rs7041	4	GC/VDBP
rs4752	4	GC/VDBP
rs222020	4	GC/VDBP
rs1352843	4	GC/VDBP
rs3733359	4	GC/VDBP
rs16847028	4	GC/VDBP

Potential New SNPs

SNP_Name	Chromosome	Gene
rs2238135	12	VDR
rs7299460	12	VDR
rs10875694	12	VDR
rs2853559	12	VDR
rs1989969	12	VDR
rs1058587	4	GC/VDBP
rs8101249	4	GC/VDBP
rs222040	4	GC/VDBP
rs221999	4	GC/VDBP
rs17219315	20	CYP24A1
rs2762942	20	CYP24A1
rs3782130	12	CYP27B1
rs10877012	12	CYP27B1

APPENDIX H: Torkko *et al. Clin Cancer Res* 2008 (May); 14:3223-9
(see next page)

VDR and *SRD5A2* Polymorphisms Combine to Increase Risk for Prostate Cancer in Both Non–Hispanic White and Hispanic White Men

Kathleen C. Torkko,[1,2] Adrie van Bokhoven,[1] Phoung Mai,[3] Joke Beuten,[3] Ivana Balic,[4] Tim E. Byers,[2] John E. Hokanson,[2] Jill M. Norris,[2] Anna E. Barón,[2] M. Scott Lucia,[1] Ian M. Thompson,[5] and Robin J. Leach[3,5,6]

Abstract

Purpose: Vitamin D and dihydrotestosterone pathways interact to promote the growth of prostatic tissue. The nuclear vitamin D receptor (*VDR*) moderates the actions of vitamin D. 5α-Reductase type II (*SRD5A2*) codes for the enzyme that converts testosterone to dihydrotestosterone in the prostate. This study tested the interactions of *VDR* (CDX2, *Fok*I) and *SRD5A2* (V89L, A49T) polymorphisms, and their associations with prostate cancer.

Experimental Design: This genetic association study included 932 non–Hispanic White (NHW) men and 414 Hispanic White (HW) men from South Texas. Cases had biopsy-confirmed cancer; controls had normal digital rectal exams and serum prostate-specific antigen levels of <2.5 ng/mL.

Results: Using logistic regression analyses to test associations with prostate cancer, only the V89L polymorphism (VV genotype compared with LL/LV) in HW men was statistically significant [odds ratios (OR), 0.64; 95% confidence intervals (95% CI), 0.41-0.99]. The interaction terms for *Fok*I and V89L in NHW men and CDX2 and V89L in HW men in the logistic model were significant (P = 0.02 and 0.03, respectively). When stratified by V89L genotype, the *Fok*I polymorphism (TT/TC versus CC) was significantly associated with prostate cancer in NHW men with the V89L VV genotype (*Fok*I OR, 1.53; 95% CI, 1.06-2.23). The CDX2 polymorphism (GG versus AG/AA) was significantly associated with prostate cancer only in HW men with the V89L VV genotype (CDX2 OR, 3.16; 95% CI, 1.39-7.19; interaction term P = 0.02).

Conclusion: Our results indicate that the *SRD5A2* V89L VV genotype interacts with *VDR Fok*I TT/CT genotypes in NHW men and *VDR* CDX2 GG genotypes in HW men to increase the risk for prostate cancer.

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doi:10.1158/1078-0432.CCR-07-4894

Prostate cancer is the most commonly diagnosed non–skin cancer and one of the 10 leading causes of death in American men (1). The etiology of prostate cancer is not well known, although both genetic and environmental factors are believed to play a role. A twin study from Scandinavia estimated that 42% of the risk for prostate cancer might be explained by heritable factors (2). A diverse range of foods and nutrients have been found to moderately affect risk for prostate cancer, including soy, isoflavones, milk, saturated fats, and tomato products (3).

A link between prostate cancer and vitamin D has been hypothesized. Lower levels of vitamin D in the serum have been associated with increased prostate cancer risk (4). *In vitro* studies have found that treating prostate cancer cells with vitamin D inhibits cell proliferation (5). Given these observations, it has been proposed that adequate circulating levels of vitamin D are important to protect against prostate cancer.

The androgen testosterone and its bioactive form, dihydrotestosterone (DHT), are necessary for the normal growth and development of the prostate, and epidemiologic evidence supports their role in the etiology of prostate cancer (6). 5α-Reductase type II is the primary enzyme that converts testosterone to DHT in the prostate (7). Men who lack the gene that codes for 5α-reductase type II have low DHT levels

and small prostates (8). Finasteride, an inhibitor of 5α-reductase type II, reduces the growth of cells from the androgen-dependent LNCaP prostate cancer cell line (9) and is associated with a decrease in tissue DHT levels (10). The Prostate Cancer Prevention Trial showed that men given finasteride had a 24.8% reduction in cancer prevalence over 7 years compared with men given placebo (11). Increased expression of 5α-reductase type II is also associated with recurrent and metastatic prostate cancer implying a role for the enzyme and DHT in prostate cancer progression (12).

The growth and differentiation of normal prostatic tissue is promoted by interactions between the vitamin D and DHT pathways (13). Levels of the bioactive form of vitamin D, calcitriol, are controlled in an autocrine fashion to regulate cell growth and decrease the risk of the cells becoming malignant. DHT seems to act as a regulator of vitamin D activity. When cells from the prostate cancer cell line LNCaP are grown in androgen-depleted medium, vitamin D no longer inhibits cell growth. With the addition of DHT, even at low physiologic levels (1 nmol/L), the antiproliferative effects of vitamin D are restored (14). It was later shown that this effect is mediated by DHT-induced suppression of 24-hydroxylase expression, the enzyme that inactivates calcitriol (15) and its precursor form (14). Additionally, in two androgen receptor–positive prostate cancer cell lines (DHT binds to androgen receptor), androgen receptor signaling was shown to be required for the vitamin D–mediated growth inhibition of the cancer cells (16). This sets up a paradox of androgens being associated with higher risk for cancer development, but at the same time being important for the anticancer activities of vitamin D.

Located on chromosome 12q13-q14, the high-affinity nuclear vitamin D receptor (*VDR*) gene mediates most of the biological activity of vitamin D (17). If vitamin D can regulate the growth of normal and cancerous prostate cells, then variations in the activity of the *VDR* may be important in the onset and progression of prostate cancer. Two of the commonly studied *VDR* polymorphisms, *Fok*I and CDX2, result in functional changes. The *Fok*I (T/C) variant alters the translation start site resulting in two isoforms of the VDR protein with differing activities (18), with the protein product from the *Fok*I T form exhibiting less transcriptional activation than the product from the wild-type C form (19). The presence of the *Fok*I C allele was found to affect immune cell behavior resulting in a more active immune system (20). The CDX2 variant in the promoter region of the *VDR* modulates promoter activity, and the CDX2 G allele, the most common allele, shows 30% less transcriptional activity compared with the A allele (21). Several studies of the *Fok*I polymorphism and its association with prostate cancer have produced inconsistent results and a meta-analysis of several *VDR* polymorphisms concluded that *Fok*I was unlikely to have a major role in prostate cancer (22). CDX2 has been less extensively studied but it was found to increase the risk for prostate cancer in men with the heterozygous genotype and high UV-B exposure (23).

The gene that codes for 5α-reductase type II, *SRD5A2*, located on chromosome 2, has several polymorphisms that have been studied for their relationship with prostate cancer. The most common polymorphism is V89L, which substitutes valine at codon 89 with leucine by a C to G nucleotide transversion. The leucine allele (L) reduces 5α-reductase activity resulting in lower DHT levels (24, 25). The A49T polymorphism results in a threonine substitution for alanine and is associated with increased 5α-reductase activity *in vitro* causing increased DHT production that may contribute to prostate cancer development or progression (26). The relationship of the V89L and A49T polymorphisms with prostate cancer has not been proven conclusively. A meta-analysis of *SRD5A2* polymorphisms concluded that the V89L polymorphism likely has no, or little, relationship to prostate cancer risk and that A49T may have a modest effect, accounting for only a small proportion of prostate cancer (27).

Because of the complex etiology of prostate cancer, the effects of many individual genetic polymorphisms are likely to be small. It is possible that larger effects may only be observed when polymorphisms are considered in combination. A polygenic model incorporating multiple loci might maximize the detection of individuals at high risk for prostate cancer (28).

The current study tested possible interactions of the *VDR* and *SRD5A2* genes as identified by two functional polymorphisms in each gene in determining risk for prostate cancer in a cohort of non–Hispanic White (NHW) and Hispanic White (HW) men from South Texas. The a priori hypotheses of this study were that the *Fok*I T allele and the CDX2 G allele, which both result in decreased vitamin D receptor activity, in combination with the V89L V or A49T T alleles, which result in higher levels of DHT, would lead to increased risk for prostate cancer. Although DHT is important for vitamin D activity and higher DHT levels might be hypothesized to reduce risk by increasing vitamin D levels, we believe that the less efficient vitamin D receptor as indicated by the presence of the *Fok*I T and CDX2 G alleles will not use the higher vitamin D levels to counter the increased risk posed by higher DHT levels.

Materials and Methods

Study population. Study participants came from the population-based prospective San Antonio Biomarkers of Risk (SABOR) for prostate cancer cohort study at the University of Texas Health Sciences Center at San Antonio, San Antonio, TX (29). SABOR began enrolling men in May 2001 to examine differences in risk for prostate cancer by race/ethnicity. Three racial/ethnic groups reflecting the diversity of the Southern Texas population were enrolled: NHW, HW, and African Americans. Only NHW and HW men were used in this study due to limited numbers of African American men (less than 65 prostate cancer cases). Race is self-identified and Hispanic ethnicity was assigned using the Hazuda model for the identification of Mexican Americans and other Hispanic ethnicities (30). The Hispanic population of South Texas is ~95% Mexican American. All participants consented to the genetic studies in accordance with the rules and regulations of the Institutional Review Board of University of Texas Health Sciences Center at San Antonio.

Cases in this analysis were men with histologically confirmed prostate cancer in the SABOR cohort, as well as men diagnosed with confirmed prostate cancer from the same clinics and health fairs from which the SABOR cohort was recruited. Gleason scores (range 2-10) were determined from chart reviews. High-grade cancers were defined as cases with Gleason scores of ≥7. Prostatectomy scoring was used preferentially over biopsy scores when available.

Controls, selected from the SABOR cohort, were eligible for this analysis if they had prostate-specific antigen values of <2.5 ng/mL at all visits (up to five annual visits) and a normal digital rectal exam at all visits. Age, defined as age at diagnosis for the cases and age at last visit for the controls, was truncated at ≥45 years old for both cases and

controls. The study population consisted of 1,346 men for a total of 585 cases and 761 controls. HW men accounted for 44% of the study sample.

Polymorphism selection and genotyping. Two *VDR* polymorphisms and two *SRD5A2* polymorphisms were genotyped: CDX2 (rs17883968; G/A) in the *VDR* promoter region and *Fok*I (rs10735810; C/T) in *VDR* exon 2, and V89L (rs523349) and A49T (rs9282858) in exon 1 of the *SRD5A2* gene.

DNA for genotyping was extracted from blood samples using a QIAamp blood kit (Qiagen). Genotyping for CDX2, V89L, and A49T was done with TaqMan allelic discrimination assays using the ABI 7900 HT Sequence Detection System (Applied Biosystems). Originally, a TaqMan assay could not be successfully designed for *Fok*I. This polymorphism was genotyped using endonuclease restriction enzyme digestion. Subsequently, a *Fok*I kit was developed and purchased. To do a quality control check on the original *Fok*I genotyping, 324 men (19% of the sample) were re-genotyped using the TaqMan kit. There was only one discrepancy between the two methodologies for an error rate of 0.3%. Applied to our larger sample of 1,685 men, this means that there were potentially 5 men who were discordant. We feel that this is an acceptable error rate and that the original methodology is validated. All genotyping was done in a molecular genetics laboratory at the University of Texas Health Sciences Center at San Antonio.

Men homozygous for each risk allele in the individual polymorphisms were compared with heterozygotes and homozygotes for the complimentary allele combined. Men homozygous for the *VDR* CDX2 risk allele (G) were compared with men with AG or AA genotypes. For the *SRD5A2* V89L polymorphism, the VV genotype was compared with LL and LV genotypes in all analyses. Due to a limited number of men homozygous for the risk alleles in the *VDR Fok*I and *SRD5A2* A49T polymorphisms, the risk genotype was combined with the heterozygous genotype and compared with men homozygous for the complementary allele. Thus, for *Fok*I, the comparison was between TT/CT and CC genotypes, and for A49T, it was between the TT/AT and AA genotypes if any TT genotypes were found.

Statistical analyses. All analyses were stratified according to ethnicity. Associations between genotypes and prostate cancer were assessed by χ^2 test (Pearson χ^2 with 1 or 2 *df*) and logistic regression analyses. All logistic regression models included age as a continuous variable. Interactions between *VDR* and *SRD5A2* polymorphisms were tested in the logistic regression analyses by adding an interaction term to the model. Nominal logistic regression was used to test the relationship of the Gleason score groups (low grade, 2-6; and high grade, 7-10) to controls as the referent group. For hypothesis testing, $\alpha = 0.05$ was used whereas 95% confidence intervals (95% CI) were computed for all relative risk estimates (odds ratios, OR). For NHW men, the study sample size had 80% power ($\alpha = 0.05$) to detect at least a 25% difference in proportions of genotypes between cases and controls based on published reports of genotype proportions in controls. For HW men, the detectable difference was 35%. Analyses were completed using SAS 9.1 statistical software (SAS Institute, Inc.).

Results

The study sample consisted of 932 NHW men (444 cases and 488 controls) and 414 HW men (141 cases and 273 controls; Table 1). Controls were somewhat younger than cases in both ethnic groups. Gleason score distribution was not different between ethnic groups.

Genotype distributions for the individual polymorphisms within each ethnic group did not differ by case-control status (Table 2). Genotype distributions for controls differed by ethnicity, however, for the *VDR Fok*I and the *SRD5A2* V89L polymorphisms. Approximately 13% of NHW controls had the *Fok*I TT genotype compared with 21% of HW controls ($P = 0.009$). For the V89L polymorphism, 52% and 44% of NHW and HW controls, respectively, had the VV genotype ($P = 0.001$). The genotype distributions in controls for these polymorphisms do not differ significantly from previously published results (31, 32). Additionally, CDX2 genotype distributions in NHW controls are similar to what was found earlier (33). There are no published data on CDX2 for HW men.

Table 1. Participant characteristics

	NHW		HW	
	Cases	Controls	Cases	Controls
n	444	488	141	273
Age (y)				
45-59	94 (21%)	182 (37%)	43 (31%)	157 (57%)
60-69	203 (46%)	185 (38%)	60 (42%)	95 (35%)
70+	147 (33%)	121 (25%)	38 (27%)	21 (8%)
Mean	66.5	64.1*	64.4	59.2*
Gleason score				
2-5	49 (15%)		10 (9%)	
6	147 (44%)		54 (47%)	
7	90 (27%)		33 (28%)	
8-10	46 (14%)		19 (16%)	
Median	6		6 †	

*$P < 0.0001$ for differences between cases and controls in both ethnic groups (*t* test).
†$P = 0.23$ for differences between NHW and HW men (Wilcoxon rank sum test).

All polymorphisms were in Hardy-Weinberg equilibrium within each ethnic group. ORs and 95% CIs for the hypothesized risk genotypes are presented in Table 2. The *SRD5A2* A49T AT genotype was compared with the AA genotype as there were no homozygous TT genotypes in the sample. Only the V89L polymorphism in HW men was marginally significant (VV OR, 0.64; 95% CI, 0.41-0.99; $P = 0.05$). No significant results were seen with the A49T polymorphism and, given the small number of men with the T allele, no interaction analyses were done with this polymorphism.

Evidence of effect modification of the *VDR Fok*I polymorphism by *SRD5A2* V89L was found (logistic regression interaction term, $P = 0.02$). When the effect of the *Fok*I polymorphism was analyzed by V89L genotype, the previously nonsignificant *Fok*I effect was significant in NHW men (Table 3). In men with the V89L VV genotype, men with the *FokI* TT or CT genotypes were at a 50% increased risk for prostate cancer (OR, 1.53; 95% CI, 1.06-2.23; $P = 0.03$). There was no evidence of interaction between *Fok*I and V89L in HW men.

There was evidence of effect modification of the *VDR* CDX2 polymorphism by V89L in HW men (logistic regression interaction term, $P = 0.03$). Men with the higher-risk V89L VV genotype combined with another higher-risk genotype, the CDX2 GG genotype, to increase risk for prostate cancer. HW men with the CDX2 GG and V89L VV genotypes have more than three times the risk for prostate cancer (CDX2 GG OR, 3.16; 95% CI, 1.39-7.19; $P = 0.01$; Table 4). There was no evidence of interaction in NHW men.

The individual polymorphisms were investigated for their associations with higher Gleason score (the measure of cancer grade). Gleason score is an important predictor of disease

Table 2. Distribution of *VDR Fok*I and CDX2 and *SRD5A2* V89L and A49T polymorphisms by case-control status in NHW cases (n = 439) and controls (n = 488), and in HW cases (n = 140) and controls (n = 273)

Polymorphism	Ethnicity	Genotype	No. (%)		P*	Genotype comparison	OR (95% CI)
			Cases	Controls			
VDR CDX2	NHW	GG	282 (64)	323 (66)	0.05	GG vs. AG/AA (ref)	0.87 (0.67-1.15)
		AG	131 (29)	148 (30)			
		AA	31 (7)	17 (3)			
	HW	GG	98 (69)	174 (64)	0.32	GG vs. AG/AA (ref)	1.57 (0.99-2.50)
		AG	38 (27)	81 (30)			
		AA	5 (4)	18 (7)			
*VDR Fok*I †	NHW	TT	67 (15)	63 (13)	0.54	TT/CT vs. CC (ref)	1.12 (0.86-1.46)
		CT	209 (47)	227 (46)			
		CC	168 (38)	198 (41)			
	HW	TT	26 (18)	57 (21)	0.73	TT/CT vs. CC (ref)	1.00 (0.68-1.57)
		CT	70 (50)	125 (46)			
		CC	45 (32)	91 (33)			
SRD5A2 V89L †	NHW	VV	230 (52)	251 (52)	0.93	VV vs. LV/LL (ref)	1.06 (0.82-1.38)
		LV	185 (42)	202 (41)			
		LL	29 (6)	35 (7)			
	HW	VV	52 (37)	119 (44)	0.24	VV vs. LV/LL (ref)	0.64 (0.41-0.99)
		LV	70 (50)	112 (41)			
		LL	19 (13)	42 (15)			
SRD5A2 A49T	NHW	TT	0 (0)	0 (0)	0.97	AT vs. AA (ref)	1.06 (0.65-1.75)
		AT	33 (7)	36 (7)			
		AA	411 (93)	452 (93)			
	HW	TT	0 (0)	0 (0)	0.94	AT vs. AA (ref)	1.32 (0.46-3.73)
		AT	6 (4)	12 (4)			
		AA	135 (96)	261 (96)			

*Pearson χ^2 test with 2 *df*.
† Significant differences in genotype distributions in controls between NHW and HW men (P = 0.009 for *Fok*I; P = 0.001 for V89L).

progression (34). Decrease in differentiation as measured by the Gleason grade is related to lack of tissue function and the Gleason score correlates with overall disease-free survival: the higher the score, the more likely that disease will recur (35). There was no evidence of associations with Gleason grade in HW men or in NHW men (results not shown).

Discussion

This study is one of the few to examine genetic risks for prostate cancer in a group of Hispanic men. Using a population of NHW and HW (largely Mexican American) men from South Texas, we found evidence of interaction between three

Table 3. Distribution of *VDR Fok*I genotypes stratified by *SRD5A2* V89L LL/LV and VV genotype groups with age-adjusted logistic regression ORs and 95% CI for associations of *Fok*I TT/CT genotypes with prostate cancer in NHW and HW men

Ethnicity	V89L Genotype	*Fok*I Genotype	No. (%)		P*	*Fok*I OR (95% CI)	P
			Cases	Controls			
NHW †	All	TT/CT	276 (62)	290 (59)	0.39	1.12 (0.86-1.46)	0.41
		CC	168 (38)	198 (41)		1.0	
	VV	TT/CT	152 (66)	142 (57)	0.03	1.53 (1.06-2.23)	0.03
		CC	78 (34)	109 (43)		1.0	
	LV/LL	TT/CT	124 (58)	148 (62)	0.33	0.79 (0.54-1.16)	0.23
		CC	90 (42)	89 (38)		1.0	
HW ‡	All	TT/CT	96 (68)	182 (67)	0.77	1.00 (0.63-1.57)	0.99
		CC	45 (32)	91 (33)		1.0	
	VV	TT/CT	40 (77)	83 (70)	0.34	1.43 (0.66-3.13)	0.36
		CC	12 (23)	36 (30)		1.0	
	LV/LL	TT/CT	56 (63)	99 (64)	0.83	0.86 (0.49-1.54)	0.62
		CC	33 (37)	55 (36)		1.0	

*Pearson χ^2 with 1 *df*.
† Interaction term in full logistic regression model for *Fok*I-V89L (P = 0.02).
‡ Interaction term in full logistic regression model for *Fok*I-V89L (P = 0.32).

Table 4. Distribution of *VDR* CDX2 genotypes stratified by *SRD5A2* V89L LL/LV and VV genotype groups with age-adjusted logistic regression ORs and 95% CIs for associations of CDX2 GG genotype with prostate cancer in NHW and HW men

Ethnicity	V89L Genotype	CDX2 Genotype	No. (%)		P*	CDX2 OR (95% CI)	P
			Cases	Controls			
NHW †	All	GG	282 (64)	323 (66)	0.39	0.87 (0.67-1.14)	0.34
		AG/AA	162 (36)	165 (34)		1.0	
	VV	GG	140 (61)	164 (65)	0.31	0.82 (0.57-1.20)	0.31
		AG/AA	90 (39)	87 (35)		1.0	
	LV/LL	GG	142 (66)	159 (67)	0.87	0.93 (0.63-1.39)	0.74
		AG/AA	72 (34)	78 (33)		1.0	
HW ‡	All	GG	98 (69)	174 (64)	0.24	1.57 (0.99-2.50)	0.05
		AG/AA	43 (31)	99 (36)		1.0	
	VV	GG	42 (81)	74 (62)	0.02	3.16 (1.39-7.19)	0.01
		AG/AA	10 (19)	45 (38)		1.0	
	LV/LL	GG	56 (63)	100 (65)	0.75	1.13 (0.63-2.02)	0.68
		AG/AA	33 (37)	54 (35)		1.0	

*Pearson χ^2 with 1 *df*.
† Interaction term in full logistic regression model for CDX2-V89L (P = 0.63).
‡ Interaction term in full logistic regression model for CDX2-V89L (P = 0.03).

functional polymorphisms from two genes in the vitamin D and androgen pathways to affect risk for prostate cancer. In NHW men, there was an interaction between the *VDR Fok*I and *SRD5A2* V89L polymorphisms to increase risk in men with the *Fok*I TT or CT genotypes and the V89L VV genotype. On the other hand, in HW men, the interaction for increased risk was between the *VDR* CDX2 GG and V89L VV genotypes.

This study examined two genes potentially involved with prostate cancer risk in combination. A polygenic approach may be a more appropriate method to study genetic associations with complex diseases such as cancer (28). The association of *Fok*I with colon cancer was seen only when analyzed in women with less than 23 CAG repeats in the androgen receptor (36). The association with prostate cancer aggressiveness of a polymorphism in a gene that codes for an enzyme involved with the degradation of DHT, 3β-hydroxysteroid dehydrogenase type II, is strengthened when analyzed by *SRD5A2* V89L genotype (37).

This study found a heterogeneity of effects according to ethnicity. Neither *Fok*I nor V89L alone were associated with prostate cancer in NHW men, but taken together, the odds for disease were increased by 50% in men with the *Fok*I TT/CT and V89L VV genotypes. No such association was found in HW men. HW men had more than three times the odds of prostate cancer if they had the CDX2 GG and the V89L VV genotypes. Previous studies have also observed the heterogeneity of effects by ethnicity with the *Fok*I polymorphism. For example, a significant trend for increasing waist-to-hip ratio with *Fok*I genotype was found in Hispanic women but not in NHW women (31).

Differences in linkage disequilibrium to unmeasured genes and/or gene-gene interactions may contribute to the differences found by ethnicity. It is possible that these differences may depend on the different combinations of these genes, or other unmeasured genes, either linked or unlinked to the *Fok*I, CDX2, and V89L polymorphisms. The findings of this study suggest that associations and interactions of the *VDR* and *SRD5A2* polymorphisms may be specific to ethnicity, arguing that research results should be stratified by race or ethnicity.

The association of the *SRD5A2* V89L polymorphism with prostate cancer ran counter to our hypothesized effect. We hypothesized that the VV genotype would be associated with increased risk for prostate cancer compared with the LL genotype because the L allele is associated with a moderate reduction in 5α-reductase type II activity resulting in lower DHT levels (24). A meta-analysis of *SRD5A2* polymorphisms, however, concluded that the V89L polymorphism likely has no, or little, relationship to prostate cancer risk (27). Most of the studies in the meta-analysis were done in NHW or African American men. Information on Hispanic men is sparse. A 2005 study in Southern California found that Hispanics with the LL genotype were at significantly increased risk from prostate cancer compared with men with the VV genotype (OR, 7.3; 95% CI, 1.5-35.5), although this finding is based on only 84 cases and 44 controls, of which only 2 controls had the LL genotype (38). In the current study, HW men with the *SRD5A2* V89L VV genotype had a reduced risk compared with the VL/LL genotypes (OR, 0.64; 95% CI, 0.41-0.99; P = 0.05). There was no association with risk in NHW men. The result in HW men was marginal, however, and may reflect a more limited sample size in HW men. These findings need to be studied in a larger cohort.

In contrast to associations with prostate cancer risk, several studies found that the LL genotype was associated with increased risk for measures of disease severity or progression (37). For example, the LL genotype was associated with more aggressive disease (39), a poorer prognosis as measured by prostate-specific antigen failure (40), and by the presence of metastases at the time of diagnosis (41). Thus, it seems that reduced DHT is associated with increased risk for disease progression (42).

HW men in this study have a higher proportion of the LL genotype (15%) than NHW men (7%). Thus, it seems that HW men are more likely to have a less efficient *SRD5A2* gene and therefore less DHT available. This could partly explain the

paradox that, overall, HW men have lower prostate cancer rates but are more likely to have higher clinical stage at diagnosis (43), poorer survival (44), and more nonlocalized disease (45) compared with NHW men. A recent study looked at the distribution of V89L polymorphisms in low-risk Inuit natives in Greenland compared with high-risk Swedish men. The proportion of the higher activity VV V89L genotype was significantly lower in Inuits compared with Swedish men (46). The authors hypothesized that this contributes to the lower risk of prostate cancer seen in the Inuits.

The cases in the SABOR study are largely prevalent rather than incident cases. Most men who were diagnosed during the up to five annual SABOR exams had probably already developed the disease that only became clinically evident during the increased surveillance as part of their participation in the study. Therefore, it is difficult to discern between markers that are associated with initiation or with progression of the disease. Long-term follow-up is needed to determine which cancer cases will progress. Although Gleason score is an imperfect measure of cancer progression, it can be useful to determine between the high-risk (usually Gleason score 7 and above) versus lower-risk cases. Even though no overall association with Gleason score was observed, the high-risk HW cases were more likely to have the V89L LL genotype (23%) than the low-risk cases (9%); there was no difference in NHW men (6% and 7%, respectively).

The presence of population stratification (genetic subgroups), particularly in HW men, could lead to inaccurate estimates of the genetic effects if the subgroups are not equally distributed between cases and controls. A recent study comparing admixture and substructure in Mexicans and Puerto Ricans, the two largest Hispanic/Latino subgroups in the United States, found population substructure in both groups (47). However, in their study of asthma, they found that this substructure only confounded their results in Puerto Ricans and not in Mexicans. The effect of population stratification may be important only if the substructure includes populations that have differential risk for the disease of interest and differential distributions of the gene of interest (48). Mexican Americans, who comprise >90% of the SABOR sample, are primarily made up of European and Native American ancestries. Native Americans are at lower risk for prostate cancer compared with NHW men (49). Only one of the polymorphisms in the current study has been examined in a native population, the Inuits in Greenland, where the proportion of the higher-activity V89L VV genotype was significantly lower in Inuits compared with Europeans (46). Depending on the percentage of native admixture in the SABOR Hispanic population and if there are different distributions between cases and controls, there could be an inaccurate estimate of the risk effect for the V89L polymorphism or the other polymorphisms in this study. Although a source of systematic bias has not been identified, a panel of ancestry-informative markers on the SABOR population is being run to study this issue.

This study found evidence that the *SRD5A2* V89L polymorphism interacts with the functional *VDR Fok*I and CDX2 polymorphisms to affect risk for prostate cancer in NHW and HW men, respectively. This illustrates the importance of examining multiple genes to understand the genetic risks for prostate cancer and the differences seen according to ethnicity. Additionally, a complex analysis may be necessary to understand a complex disease. Because genomewide linkage studies found strong locus heterogeneity of prostate cancer susceptibility genes (50), prostate cancer is not likely caused by a few genes but by multiple genes from different pathways. Therefore, a more complex analysis looking at interactions between genes rather than a single gene analysis may be necessary to understand complex diseases like prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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